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Charles R. Thomas, Jr.
Kumar Alagappan
Editors

Oncologic Emergency Medicine

Principles and Practice

Second Edition

Springer

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This book is dedicated to my wife, Courtenay Carmody, and my two sons, Samuel and Benjamin, whose love and support bring great joy to my life and purpose to my work.
In memory of my mother, Mary Kate Todd, who left us much too early.

–Knox H. Todd

To my supportive wife, Muriel Elleen; our wonderful two children, Julian Franklin and Aurielle Marie; our parents; and siblings for their love and support of my career path.
In memory of my mother, Ruth Marie Wilson Thomas, who fought gallantly in the war against cancer and whose prayers have blessed me over the past five decades.

–Charles R. Thomas Jr.

This book is dedicated to my wife, Bridget Shields, and my two daughters, Lakshmi and Jyothi.
In memory of my father, Alagappa Alagappan PhD, an international civil servant who traveled to 95 countries. He always felt that learning was a treasure that would follow its owner everywhere.

–Kumar Alagappan

Foreword

This second edition of *Oncologic Emergency Medicine: Principles and Practice* has broadened the scope of emergency care for the oncological patient and rightfully so. More patients are living with cancer than ever before. Many cancer diagnoses are associated with greatly extended lifespans. With greater lifespan, cancer survivors are also at risk of acquiring complications from their past medical, radiation, or surgical care, in addition to an underlying cancer.

Today's patient living with a current or prior cancer diagnosis lives within a network of health care providers. The emergency physician and the oncologist must understand not only the underlying pathophysiology of the disease and its treatment, but also appreciate how patients present in distress and how care is optimized to meet the needs of the patient. Indeed, while using best practice options, the team of health care providers personalizes each patient's treatment, stabilization, and recovery to optimize outcomes, seeking to match the expectations of the patient and family.

In this edition, cancer prevention approaches are discussed. Emergency physicians must be comfortable with cancer prevention approaches to minimize future risk for those living with cancer. As in the first edition, the text provides cutting-edge information related to specific oncologic conditions which may present in the emergency department. At times these conditions may be the initial presentation of the cancer. Other times these conditions may represent complications of therapy, disease progression, and/or secondary infection. Many of these conditions require a time-dependent response to minimize additional morbidity or mortality. This text provides unique information (including discussion of new immunologic therapies) that may be covered only superficially by other books or articles in the field.

The palliative aspects of cancer care are also covered. The learning points covered in these chapters are especially cogent in today's changed world of opioid dependence and COVID-19. Guidance is provided regarding the management of pain, communication about the diagnosis/progression of cancer, and discussions regarding hospice and other related factors. These represent key components of doctoring which require great skill and understanding of the patient, as well as the disease.

This edition also seeks to extend our understanding of health disparities and vulnerable populations, international approaches to oncological emergencies, and other topics on the cutting-edge cancer research, treatment, and management. The editors are to be congratulated for extending their earlier work and both recognizing and anticipating the needs of care providers in oncologic emergency medicine. They have provided a powerful tool to enhance the care provided to cancer patients.

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Preface

It is with renewed excitement that we present the second edition of *Oncologic Emergency Medicine: Principles and Practice*, the major comprehensive textbook in this emerging field. Against the backdrop of rising numbers of cancer patients and survivors as the US population ages, and of a forecast shortage of cancer care providers, this book is designed to serve as the most authoritative, single-source clinical reference on oncologic emergencies. This comprehensive text was specifically designed to address the complexities of understanding and managing cancer emergencies, with an emphasis on increasing communication and collaboration between emergency physicians and the multiple providers who participate in caring for those with cancer.

The expanded cadre of contributors to the second edition includes a broad spectrum of experts in emergency medicine and nursing, surgical and medical oncology, hematology, diagnostic and interventional radiology, palliative care, psychiatry, critical care, dermatology, ophthalmology, clinical pharmacy, addiction psychology, social work, and health services research.

Emergency departments account for approximately one-half of all hospital admissions, and this proportion is even greater for those with cancer. While the largest portion of the book focuses on a number of clinical oncologic emergencies and their varied presentations to the emergency department, this text offers the opportunity to address more broadly and systematically the vantage point of emergency physicians who work in a critical hub of patient care: the emergency department. Emergency department visits resulting from disease progression as well as toxicities of anticancer treatments serve as an important patient-oriented metric of cancer care quality. This text emphasizes the critical importance of emergency department care within a comprehensive cancer treatment system. The principles of care will be similar whether the emergency department is in a dedicated clinical cancer care facility or a matrix care structure. The methods of executing best practices may differ based on the structure of the cancer care system; however, the vast majority of emergency care for those with cancer is similar across emergency department settings, whether in academic, community, or hybrid practice. The text is structured to cover multiple fundamental areas of emergency care:

Part I is centered on systems issues in oncologic emergency medicine. We discuss the epidemiology of oncologic emergencies, existing models of emergency department care, informatics, the evolving role of quality measures, patient navigation, and the importance of emergency nursing and social work.

Part II considers the role of emergency medicine in primary and secondary cancer prevention, including smoking cessation, alcohol exposure, ionizing radiation and cervical cancer prevention and detection, as well as screening for lung cancer, colorectal cancer, and melanoma.

Part III will seem perhaps the most familiar to readers and includes a discussion of the evaluation and treatment of a variety of oncologic emergencies, organized by organ systems. This section also covers specific conditions common to many cancer types, including febrile neutropenia, thrombosis, and bleeding.

Part IV examines important issues related to treatment toxicity, including chemotoxicity, radiotoxicity, and post-surgical complications, as well as transplant-related issues and toxicities of novel antineoplastic agents such as checkpoint inhibitors and CAR T-cell therapy.

Part V addresses palliative care issues pertinent to the intersection of emergency medicine and oncology. This section discusses end-of-life care, including the role of palliative surgery, the management of symptoms in those with advanced cancer, approaches to opioid analgesic use (and misuse), and the significance of emergency department use at the end of life.

Part VI deals with contextual issues critical to the subdiscipline of oncologic emergency medicine. It incorporates a chapter on the challenges to emergency medicine and oncology posed by COVID-19 and considerations of ethics, health disparities, and ongoing efforts to advance research and education. Finally, we conclude with a chapter by physicians regarding their personal experiences with cancer.

An added feature to this edition are board review questions accompanied by brief and concise explanations of the answers.

The editors and associate editors are extremely proud of this second edition of *Oncologic Emergency Medicine: Principles and Practice* and we wish to thank all of the contributors who have given their time, insight, and experience to create a truly unique text that will serve as a valuable resource for practitioners, researchers, policy makers, trainees, payors, and administrators, as we care for those with urgent cancer needs. We would like to give a special acknowledgment to Ms. Katherine Kreilkamp of Springer for her efficient and diligent role in textbook development. We are deeply indebted to her and to Springer for their support.

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Part I

Systems

Epidemiology

1

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Overview

Improving the quality of cancer care and reducing preventable health system use are goals of increasing importance to health practitioners and policy makers in the United States (US) and internationally [1–3]. In 2020, it is estimated that over 1.8 million new cases of cancer will be detected in the United States, over 600,000 deaths will result from cancer, and the estimated annual cost of cancer care is expected to reach to more than $170 billion [4, 5]. Globally, the incidence of cancer is expected to increase more than 60%, to nearly 30 million, between 2020 and 2040 [6]. Furthermore, as global cancer incidence increases, the burden of cancer care is expected to fall increasingly on low-income countries [7]. This will have significant impacts for the healthcare systems in all countries as they address access to primary and specialty for a growing number of oncologic patients.

In the United States, emergency departments (EDs) serve as a significant source of urgent and safety-net care. In 2014, there were 137.8 million ED visits, reflecting an increase of nearly 15% compared to 2006 [8]. Over the last decade, there has been increased scrutiny of EDs as a source of potentially preventable care because of the high cost of care, potential delays in care, and crowding concerns. As policy makers and practitioners strive to improve quality and reduce fragmentation of cancer care, reducing ED visits is frequently a goal of care coordination program and cost reduction effort. There is a particular interest in reducing visits for concerns labeled as "avoidable" or "preventable"; however, no consensus definitions exist to define or identify such visits [9–12].

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Approximately 4% of all adult ED visits in the United States are for cancer-related complaints [13]. Reports from Australia, the United Kingdom (UK), Brazil, and South Korea highlight concerns about the growing number of cancer patients and the increasing burden of care on EDs in the management of unscheduled care [9, 14–16]. A 2017 National Health Service (NHS) report emphasizes similar patterns in the United Kingdom with dramatic increases in ED presentations related to cancer and concomitantly high rates of inpatient admissions—often associated with poor patient experience, poor coordination of care, poor communication, and fragmented patient care pathways [17].

Oncologic patients present for care in the ED at all points across the cancer care continuum from diagnosis through treatment, survivorship, and end-of-life (Fig. 1.1) [1]. ED visits in this population can range from medical emergencies for those undergoing cancer treatment to nonurgent administrative decisions such as sending a patient to the emergency department for hospital admission. Symptoms—related to cancer or its treatment—may play a role at all points across the continuum; similarly, oncologic patients may present to the ED for concerns or events that are completely unrelated to their cancer (e.g., motor vehicle collisions, musculoskeletal injuries, lacerations, etc.). Importantly, oncologic patients may incur multiple visits for the same issue or for different reasons.

ED use for oncologic patients reflects a complex interaction of individual and contextual factors—including provider behavior, health system characteristics, and health policies. This complexity is well characterized by Chen et al., who show interrelated causal loops to describe a broad array of factors that influence ED use in this population—individual factors (e.g., access to care/insurance, ability to use services), provider factors (e.g., knowledge, skills, communication, referrals, and access to specialists), health system factors (e.g., bed capacity), and policy factors (e.g., availability of social care) (Fig. 1.2) [18]. While these causal loops are identified based on research derived from the United Kingdom, in the context of a national healthcare system,

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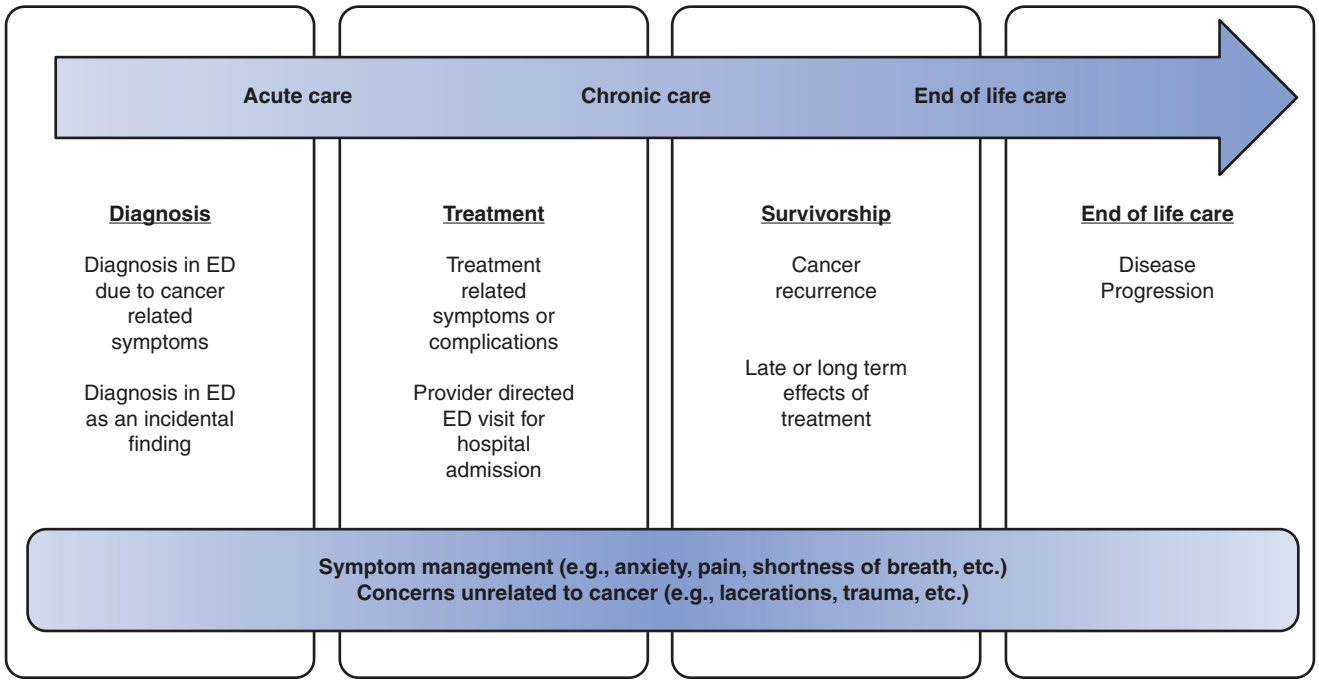

Fig. 1.1 Emergency department visits across the cancer care trajectory, modeled on the Institute of Medicine's continuum of cancer care [1]

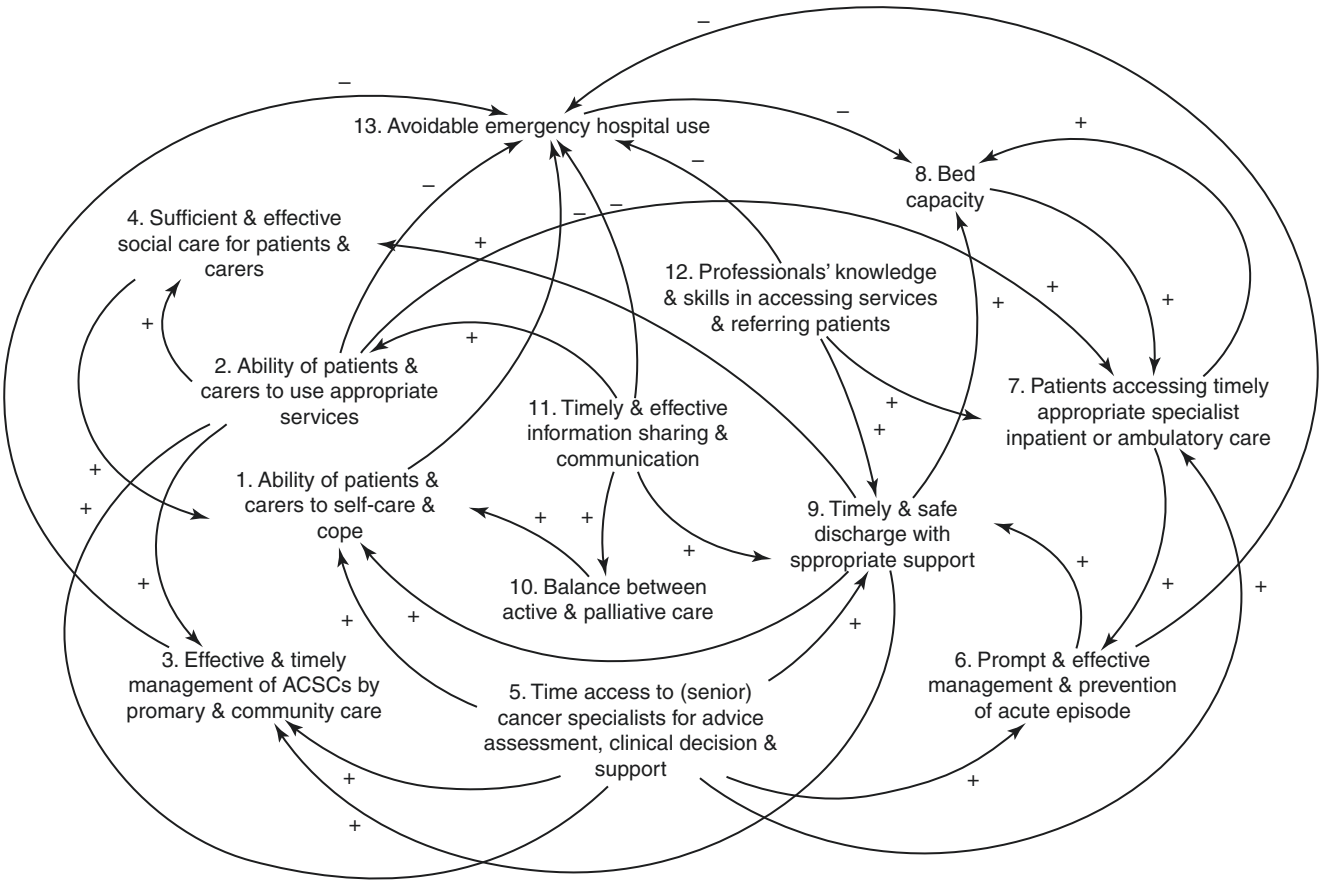

Fig. 1.2 Causal loop diagram of factors that influence ED use by oncologic patients. (From Chen, et al. [18] with permission CC by 4.0)

similar factors apply to ED use across settings. In the United States, access to care is further influenced by insurance status and an individual's ability to pay for care—factors which hold less influence in settings with nationalized healthcare systems.

Early investigations of the ED role in cancer care focused on cancers that were diagnosed in the ED and therefore represent a failure of outpatient detection and potential treatment delays [19, 20]. While these factors remain of concern, more recent studies have moved to enumerate visits in cohorts of patients, describe the type of care provided, and identify potentially preventable ED use [10, 13, 21–23]. Despite these efforts, the epidemiology of ED use by oncologic patients, including patterns and determinants of use, remains poorly understood. Few studies describe the incidence of ED use by cancer patients across cancer types, in population-based samples, and even fewer explore the burden of cancer visits experienced by patients or by ED providers [11]. Numerous studies examine complications, hospital admission, and/or readmission rates for specific cancers, treatment regimens, or procedures, but few of these examine how readmission or complications impact emergency department use [24–31].

In light of the importance of ED visits in the care of oncologic patients, this chapter reviews what is known about ED use among oncologic patients, specifically:

- Distribution (i.e., frequency, incidence, and disposition) of visits
- Determinants of use
- Preventability of visits

Distribution of ED Visits Among Oncologic Patients

Data Sources

In the United States, data sources capturing cancer type, cancer stage, treatment, and health system utilization are not robust. For example, administrative datasets capturing healthcare utilization data may not include cancer diagnosis, treatment information, or complete comorbidity data (e.g., Medical Expenditure Panel Survey (MEPS) [32], Nationwide Emergency Department Sample (NEDS) [33], National Hospital Ambulatory Medical Care Survey (NHAMCS) [34]). Likewise, cancer registries collect robust specific cancer and initial treatment information; however, they may not capture full health services utilization data, including ED visits [35]. The Surveillance, Epidemiology, and End Results (SEER) program includes population-based information about cancer incidence and survival but does not provide related health services data [36]. While researchers may link available datasets to reduce these gaps in information, limitations in diagnosis, treatment, or health service use remain. Therefore, the frequency and incidence of cancer patients visiting EDs in the United States is difficult to ascertain, particularly for large population-based samples [11].

Studies of the incidence and frequency of ED use by cancer patients are based on either the visit-level or patient-level unit of analysis. Visit-level analyses, for example, provide information about the quantity of care provided to cancer patients by EDs and indicate which diagnoses are associated with the visits. Visit-level analyses may not account for multiple visits made by the same patient, and these datasets may lack patient-specific information, such as diagnosis and treatment data. Patient-level analyses, in contrast, can identify characteristics of patients associated with ED use, thus providing more insight into determinants of health system use.

Estimates

Cancer-Related ED Visits In the United States, it is estimated that over 4% of all ED visits are for cancer-related reasons [13, 21]. Geographically, patterns of ED use are consistent across regions of the country (Northeast, Midwest, South, West) [21]. The number of ED visits varies by primary cancer diagnosis. The top cancers associated with ED visits include lung, 10–27% [13, 22, 23, 37, 38]; breast, 6–15% [13, 22, 23, 37, 38]; colon, 6–12% [13, 22, 23, 37, 38]; prostate, 5–11% [13, 22, 23, 37, 38]; multiple cancers, 10% [13]; and female reproductive or genital, 6–7% [13, 22, 23].

Incidence of ED Use Among Oncologic Patients Among all oncologic patients, the presence of any ED visit and the distribution and timing of ED visits are not well established, in part, because estimates depend on a specific precipitating potential triggering event under study. For instance, ED visits may be measured within a particular time frame (e.g., from diagnosis or from treatment, such as surgery, radiation, or chemotherapy), and the time frames vary greatly in the literature [11]. For example, one study of breast cancer patients receiving a mastectomy reported that 3% of the sample had an ED visit within 30 days of surgery [39], while 11% of high-risk patients with head and neck cancer receiving radiation had an ED visit during treatment or within 90 days of treatment completion [40].

Using a standardized 30-day visit rate, studies that examined postsurgical periods reported 2–12% of the sample visited an ED within 30 days after surgery, and a study that evaluated a post-chemotherapy time frame demonstrated 5% of the sample visited the ED [11]. Estimates provided by the

few available population-based studies tend to report higher ED use than those that focus on smaller within-setting study samples [11].

Time from diagnosis offers a consistent measure to examine ED use by oncologic patients across cancer types, although it is important to consider the factors that impact time to diagnosis. As expected, based on differences in diagnostic and treatment patterns, the incidence of ED visits varies by cancer type. Estimates of ED use by cancer type and time from diagnosis at 30, 180, and 365 days from diagnosis are provided in Table 1.1 [23, 41–43].

Multiple Visits A large proportion of cancer patients have multiple ED visits. Between 2009 and 2010, among patients with all cancer types in California, 20% had one ED visit, 8% had two visits, and 7% had three or more visits within 180 days of diagnosis. Among those with at least one ED visit, 44% had two or more visits and 21% had three or more visits [23]. In a national sample of colon cancer patients who visited the ED (55%), 24% had two visits and 25% had three or more visits within 1 year of diagnosis; importantly, those with three or more visits (14% of the sample) accounted for over half the total number of visits [43]. Not surprisingly, these rates of multiple visits are substantially higher than in the general US population where 6.5% have two or more visits to an ED annually [44].

Table 1.1 Cumulative percentage of cancer patients with at least one ED visit by time from diagnosis[a]

	Time from diagnosis		
Cancer type	30 days	180 day	365 days
All	17	35, 44–69 [41]	44
Bladder	21	44	54
Brain	39	60	68
Breast	5	22	31, 15–21 [42]
Colon	20	41	49, 55 [43]
Digestive	26	54	63
Endocrine	7	19	25
Eye	6	18	26
Gynecological	17	36	44
Hodgkin lymphoma	18	43	46
Ill-defined/unknown	36	53	57
Leukemia	26	45	53
Liver	29	54	63
Lung	30	55	64
Male genital (non-prostate)	16	28	36
Melanoma	5	14	22
Myeloma	28	53	63
Non-Hodgkin lymphoma	22	44	51
Oral	12	39	48
Other	20	42	53
Pancreas	37	62	69
Prostate	6	17	25
Respiratory (non-lung)	18	43	52
Stomach	27	55	63
Urinary	21	39	47

[a]These estimates are from four population-based studies that provide data on ED visits by cancer patients and time from diagnosis. Unless specified, data are derived from California's state-based data from 2009 to 2010 [23]

Disposition While inpatient admission rates vary by cancer type, patients with cancer who visit the ED tend to have higher rates of admission (49–63%) and are more than twice as likely to be admitted than non-cancer patients [13, 21, 23, 37, 45].

International Perspective on the Incidence and Frequency of ED Use ED use by cancer patients outside the United States is also characterized by high frequency and incidence. For example, during a 1-year study period at a hospital in Japan, 8% of individuals who visited the ED had a cancer diagnosis [46]. Reports from Australia indicate that 40% of cancer patients visited the ED at least once in the year following diagnosis, and 2.4% of all ED visits were made by cancer patients [47, 48]. One single-site study from Australia reported 38% of breast cancer patients receiving chemotherapy presented to the ED within 30 days of chemotherapy administration [49].

Similarly, over 53% of women in Ontario, Canada, who completed at least one cycle of chemotherapy for breast cancer had an ED visit within 30 days of treatment [50]. Among Canadian women over the age of 65 undergoing surgery for breast cancer, 13% had an ED visit within 45 days of surgery [51]. Another Canadian study examining ED use for head and neck cancer patients undergoing surgery found 8.4% visited in ED within 30 days of surgery [52]. These studies demonstrate that despite an indication of high ED utilization by oncologic patients internationally, similar methodological issues persist, and direct comparison of study results across countries is complicated by a focus on different cancers, conditions, treatments, contexts, and time frames of ED use.

Likewise, studies outside the United States report high frequencies of patients with multiple ED visits. In Taiwan, 12% of cancer patients who visited an ED had multiple visits in a 1-year study period, and for those specifically with head and neck cancer, nearly 70% had more than one ED visit over a 12-year study period [53, 54]. A report from the Bureau of Health Information in New South Wales, Australia, indicates that 10% of cancer patients make three or more visits in the year following diagnosis [48]. A separate Australian study found that up to 63% of cancer patients visiting the ED had multiple visits [47]. Among Canadian breast cancer patients receiving chemotherapy, nearly 37% of those within an ED visits within 30 days of treatment had multiple visits [50].

Determinants of ED Use Among Cancer Patients

The Andersen Behavioral Model of Health Services Use provides an important framework to understand the determinants of ED use among cancer patients [55]. Specifically, in this model, health service use is determined by the complex interaction between predisposing characteristics, enabling resources, and need factors. Predisposing characteristics include demographic factors, individuals' beliefs, and aspects of social structure which are not intended to directly explain but rather to help understand differences in the use of health services [55]. Enabling resources include individual and family factors (e.g., income or health insurance) and community characteristics (e.g., region of residence). Need or illness-level factors include both perceived and evaluated health status including symptoms and diagnoses.

The predisposing, enabling, and need factors associated with ED use and frequent ED use tend to be similar across the literature—whether in studies of specific chronic conditions such as diabetes or those limited to subpopulations such as older adults [56, 57]. In the US general population, predisposing factors associated with higher ED visit rates include age and sex, with higher rates among adults age 65 years and older age and among females compared to males; rates are lower among those living in the West compared to other regions [8]. Enabling factors associated with higher rates of ED use include private insurance and Medicaid compared to Medicare or no insurance and residence in low-income areas [8]. In terms of need, a medical diagnosis—including abdominal pain, chest pain, back problems, urinary tract infections, or skin infections—is most often listed as the primary concern for an ED visit [8].

Identifying predisposing, enabling, and need factors for ED visits among oncologic patients presents challenges due to the previously discussed methodological issues including differences in study populations (e.g., by cancer type, country of residence), treatment, the complications of interest, and time frame studied. Among US studies, there is great heterogeneity in the time period examined (e.g., in the first year after diagnosis vs. within 30 days of treatment), the number of participants (n = 220 to 89,311), and diagnoses included [11, 43]. Some studies focus on older adults precluding the ability to examine age as a determinant of ED use. Many of the available studies focus solely on one or more of the top four most prevalent cancers (i.e., prostate, breast, lung, and colorectal).

Predisposing Factors

Significant predisposing factors for oncologic patients of increased ED include race, age, and gender. Specifically, nonwhite [43] and African American [56, 58] compared with white, non-Hispanic race/ethnicity and older age compared to younger age [43, 56] were associated with more ED use. Additionally, being male compared to female sex resulted in increased rates of ED use [59, 60].

Enabling Factors

As in the general population, enabling factors associated with increased ED use for oncologic patients are area of residence and income level in the community of residence, insurance status, and marital status. Those with urban and metropolitan compared to rural residence had higher levels of ED use [56]. Being eligible for Medicaid due to blindness or disability [61], or residing in a state in which Medicaid copayments increased and prescription drug and other benefits were reduced [41], was associated with more ED use. Being unmarried compared to married [56] and residing in a census tract with low median income [56] were also associated with increased ED use.

Need Factors

Multiple conceptualizations of perceived or evaluated health status are associated with ED use in cancer patients in current literature. Operational definitions of need include reasons for visits, symptoms, chief complaints, and diagnoses and vary across healthcare settings and studies. Ultimately, the underlying symptoms or diagnoses associated with ED visits are need-related determinants of ED use. Cancer patients present to the ED with a variety of complaints but tend to have symptoms or diagnoses related to pain, pulmonary, gastrointestinal, cardiac, and infectious concerns.

A systematic review of symptoms experienced by cancer patients visiting the ED identified 28 reported symptoms, including psychological (such as anxiety), gastrointestinal, neurological, respiratory, dermatological, and urological symptoms, pain, fever and infection, edema, bleeding, fatigue, and altered nutritional status [62]. The primary reasons for visits defined as chief complaints (not diagnoses) for oncologic patients tend to be related to pain, respiratory distress, fever, and gastrointestinal issues [21, 37, 45].

In recent population-based studies, diagnoses (most frequently ICD9 or ICD10) are generally used to identify "reasons" for an ED visit [10, 13, 23]. In a national sample examining cancer-related ED visits between 2006 and 2012, pneumonia was the single diagnosis associated with the most ED visits, accounting for 4.5% of cancer-related ED visits [13]. Diagnoses that each represented between 3 and 4% of visits were nonspecific chest pain, urinary tract infections,

septicemia, and chronic obstructive pulmonary disease [13]. Abdominal pain, fluid and electrolyte disorders, congestive heart failure, cardiac dysrhythmia, and intestinal obstruction without hernia each represented between 2 and 3% of the diagnoses for ED visits by cancer patients [13].

Importantly, diagnoses differ by the disposition of the visit (e.g., to home vs. inpatient admission). In California, the top three diagnoses for ED visits made by individuals within 180 days of cancer diagnosis who were admitted to the hospital were septicemia (8%), cardiovascular problems (7%), and complications from surgery (5%), whereas the top three for visits that resulted in discharge home in the same sample were abdominal pain (7%), cardiovascular problems (6%), and urinary, kidney, and bladder complaints other than a urinary tract infection (5%) [23].

Regardless of visit disposition, the top ten diagnoses cumulatively account for less than 40% of all visits, underscoring the variability and complexity in precipitating factors for ED visits among cancer patients [13, 23]. Furthermore, ICD codes are limited in their ability to capture precipitating factors associated with ED use; moreover, the specific codes selected to categorize diagnoses into clinically meaningful groups vary with different algorithms used to group ICD codes to represent, for instance, surgical complications or chemotherapy-related complications.

Additional studies identify need factors associated with ED use including comorbidities, specific treatments, time to treatment, cancer stage, and survival. ED use is increased among patients having a greater number of comorbidities [43, 61, 63], a diagnosis of depression compared to no depression [64], and a radical prostatectomy compared with no treatment [56], having external beam radiation therapy with androgen deprivation therapy or external beam radiation therapy plus brachytherapy compared to radical prostatectomy [65], and having no therapy compared to radiation therapy [43, 58] and in those experiencing more severe symptoms [63], those surviving less than 1 year from diagnosis compared to surviving 1 year or more [59], and those receiving chemotherapy versus no chemotherapy [43, 61]. Cancer stage is also considered a need factor that could influence ED use. However, evidence of the impact of cancer stage on more or less ED use is unclear [11]. Additionally, among African American men with a prostate cancer diagnosis compared to white men, having a longer time to treatment was also a determinant of ED use [58].

International Perspective on Determinants of ED Use

The reasons for ED visits reported in international studies are similar to those reported in US studies. A single-site study from Brazil found the most common complaints were abdominal pain (18.4%), back pain (8.5%), dyspnea (8.5%), weakness/fatigue (8.1%), fever (7.0%), and nausea/vomiting (4.8%) [66]. A separate single-site Australian study which focused on breast cancer patients receiving chemotherapy found the most common reasons for an ED visits were non-neutropenic fever presentations (27%), neutropenic fever (24%), pain (14%), drug reaction (10%), and infection (6%) [49]. A Canadian population-based study of ED visits for women over the age of 65 years undergoing curative surgery for nonmetastatic breast cancer identified diagnoses associated with visits to be infectious disease (19%), musculoskeletal trauma/wound (13%), other (12%), surgical site issues (12%), process of care (4%), and other noninfectious diagnoses (40%) [51]. In Taiwan, Tsai et al. found pain (27.8%), fever (11%), shortness of breath (9%), abdominal distention (4.6%), and nausea/vomiting (4.2%) to be the most frequent presenting complaints [54].

Identified predictors of ED use are more robust in some international studies, likely due to comprehensive health service use data available in nationalized health systems. In a UK study including all cancer diagnoses, Abel et al. evaluated predisposing, enabling, and need factors associated with increased ED use finding the following independent predictors: women diagnosed with cancers of the bladder, brain, colorectal, stomach, and lung; men diagnosed with oral cancer, lymphoma, and melanoma; younger age compared to older age for acute leukemia and colon, stomach, and esophageal cancers; older age compared to younger age for laryngeal, thyroid, oral, and Hodgkin lymphoma and melanoma; low SES for most cancers, especially oral, anal, laryngeal, and small intestine cancers [67].

An examination of ED visits made by cancer patients in New South Wales, Australia, found that having neurologic or lymphohematopoietic cancers (compared to the skin), having comorbidities, and living in a socioeconomically disadvantaged area increased the likelihood of an ED visit [48]. Dufton et al. identified being born outside Australia and cancer diagnoses of the head and neck, upper gastrointestinal, colorectal, lung, skin, or breast as determinants of ED use [16]. In a population-based sample of older breast cancer patients in Canada, Westley et al. reported significant determinants of ED visits, within 45 days of surgery, were localized or regional versus in situ disease, mastectomy versus lumpectomy, operation before definitive oncologic control, lower institutional volume, having more than five prescriptions, benzodiazepine use, anticoagulant use, cardiovascular disease, diabetes, past hospitalization, and lower income [51].

Preventability of ED Visits Among Cancer Patients

One of the primary purposes of examining reasons for ED visits is to determine whether or not care could have been prevented or more optimally delivered in an alternate setting.

Despite persistent attention to preventable ED use, there is no consensus definition, generally, or applied specifically to oncologic patients [11]. Two previous approaches used to identify potentially preventable or avoidable ED visits are the Agency for Healthcare Research and Quality's classification of Ambulatory Care-Sensitive Conditions (ACSC, now referred to as Prevention Quality Indicators) and the New York University's Billings algorithm [68, 69]. Both of these methods use discharge diagnoses to determine and define the reason for a preventable visit. The ACSC identifies 16 conditions that are considered potentially preventable with proper primary or ambulatory care. The Billings algorithm categorizes visits into four groups: nonemergent, emergent but primary care treatable, emergent with ED care needed but potentially avoidable if timely and effective ambulatory care had been available, and emergent when ED care was truly needed and the visit was not preventable [68]. Using such definitions, it is estimated up to 56% of all ED visits (not restricted to cancer patients) can be considered avoidable [70, 71].

Neither the ACSC nor Billings classifications are oncologic specific, and they may not adequately capture preventable use among oncologic patients. As an example, febrile neutropenia, a common chemotherapy-related side effect, is not included in either method [10, 11]. In an attempt to capture cancer-specific diagnoses, in 2016 the Centers for Medicare & Medicaid Services (CMS) established a quality metric that identifies diagnoses associated with potentially preventable ED use by cancer patients—including anemia, dehydration, diarrhea, emesis, fever, nausea, neutropenia, pain, pneumonia, or sepsis within 30 days of outpatient chemotherapy treatment [72].

Using claims data, Panattoni et al. developed a specific method to identify potentially avoidable use among oncologic patients and specified 18 diagnoses from either the CMS proposed Admissions and Emergency Department Visits for Patients Receiving Outpatient Chemotherapy Measure and/or the Symptom Tracking and Reporting PRO tool as representing potentially preventable ED visits in the year after chemotherapy, radiation, or both [10]:

- Anemia
- Appetite loss
- Constipation
- Cough
- Dehydration
- Diarrhea
- Dyspnea
- Dysuria
- Emesis
- Fatigue
- Fever
- Flushing
- Nausea
- Neuropathy
- Neutropenia
- Pain
- Pneumonia
- Sepsis

Using these potentially preventable diagnosis codes, they identified pain, fever, and dyspnea as the most prevalent potentially preventable diagnoses for cancer patients, accounting for approximately 40% of ED visits using primary diagnosis coding, and over 63% if all coding place fields were included [10].

When considering the specific diagnoses included in these methods, the concept of what is preventable remains ambiguous. Certainly, diagnoses such as sepsis, pneumonia, or dyspnea may represent clinically significant events that justify treatment and possibly admission to the hospital. Given that the diagnoses listed above may be present in over half of cancer-related ED visits but these patients might actually have serious life-threatening conditions, risk stratification methodologies are needed to truly identify patients where ED visits could be safely avoided [10, 22]. A particularly unique event to consider is patients who obtain their initial diagnosis in the ED, which is estimated to occur in 12–32% of oncologic patients [67, 73–75]. In these situations, the reason for the visit may have been directly related to symptoms that led to a diagnosis or could have been an incidental finding during the treatment of an unrelated complaint. In either circumstance, it is difficult to establish whether these visits were potentially avoidable based on diagnosis codes and even more difficult to determine if limited access to care or cancer screenings contributed to a diagnosis in the ED.

International Perspective on Preventable ED Use

Identifying potentially preventable ED visits is also challenging in international settings. Some literature, particularly from nationalized healthcare systems, focuses on a cancer diagnosis in the ED as a particular subset of preventable ED use [74, 76]. This may be a useful indicator of overall cancer care and screening in a health system, yet as described above, the ability to establish the true preventability of those visits is unclear. In a population-based Canadian study, Barbera et al. report that nearly 7% of visits were potentially avoidable and based on a definition of avoidable care that encompasses device problems, constipation, repeated prescriptions, follow-up visits, or laboratory examinations [77].

A single-site study from France specifically examined the appropriateness of referrals (based on the need for medical exam within 24 hours) to the ED for oncologic patients and the potential preventability of those visits based on presenta-

tion and treatment [78]. In this study, 33% of visits were categorized as having a high likelihood of being avoidable and 14% as having a moderate likelihood of being avoidable. Individual chart review was used to identify the driving factors for each visit (e.g., care provided at a preceding healthcare contact, an issue with a previous discharge process, patient not understanding a plan of care, etc.) to establish the likelihood of a visit being avoidable. Similarly, Oh et al. examined ED visits in a single South Korean hospital using expert review of medical records to determine if visits met the criteria they considered avoidable. They defined avoidable as a problem that could be resolved at a primary care office, out-patient clinic, or over the telephone and considered visits due to hospice referral, chemotherapy or radiotherapy, or surgery as unavoidable. Among the most common chief complaints (i.e., pain, GI symptom, dyspnea, altered mental status, other neurologic symptom, fever/chills, bleeding, edema/swelling, general weakness, urinary symptoms or constipation, and URI symptoms), the percentages of avoidable and non-avoidable visits varied within each category [15]. For example, 60% of visits for pain were classified as avoidable, while 40% were unavoidable. Likewise, 53% of visits for dyspnea were deemed avoidable, while 47% were unavoidable.

Ultimately, the ability to evaluate ED visits and the extent to which they are potentially avoidable are dependent on a country's health system and available data sources. Even in countries with robust national health systems and data collection processes, defining avoidable ED visits remains a problem, particularly for the oncologic patient population. It should be noted that approaches requiring extensive individual chart review would be difficult to apply to population-based samples. Consensus definitions of avoidable visits and efficient, effective care systems for oncologic patients are important internationally; however, further work is needed to reach these goals.

Conclusion

One of the greatest ongoing challenges to providing high-quality cancer care, for the United States and internationally, is the management of acute complications of cancer and rapidly developing treatments [79]. The need for well-coordinated care for end-of-life and palliative care is well established, but there is also a need to address acute oncologic needs [3]. Evaluating ED use by oncologic patients requires examination of both the incidence and frequency of visits by cancer patients. By understanding the volume of care provided by EDs, as well as the percentage and types of visits, health providers and systems are better able to prepare for the required treatments and partner with policy makers to establish consensus definitions of preventable and non-preventable ED use in this population. This information is essential to developing successful innovative oncologic care models which may include interventions such as telemedicine, enhanced symptom management support systems, care pathways, and oncologic-specific urgent care or emergency departments.

EDs provide a significant amount of care for oncologic patients, with 4% of all ED visits categorized as cancer related and over 40% of cancer patients having at least one ED visit within a year of diagnosis. While a few select hospitals and health systems have developed oncologic-specific EDs, urgent cares, or walk-in clinics to address unscheduled concerns, the majority of patients receiving cancer treatment must rely on general EDs for acute and unscheduled needs [3].

Determinants of ED use include a complex constellation of predisposing, enabling, and need factors, with most studied at the individual level. Less is known about broader contextual determinants of ED use in cancer patients—including provider, health system, and health policy factors—in part because of limitations in extant data to study ED use in oncologic patients. Future research is recommended to address these gaps. Based on available data, definitions of truly preventable and avoidable ED visits remain unclear. However, available data demonstrate the magnitude of potentially avoidable visits may be significant and warrants further investigation. Furthermore, examinations of reasons for visits for symptoms including pain, dyspnea, nausea, and concerns for bacterial infection may have a significant impact on enhancing cancer care, and addressing these concerns may help to reduce unnecessary ED visits [22].

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Models of Care

2

Michael G. Purcell

Introduction/Background

Both the emergency medicine and oncologic communities recognize that cancer patients require specialized emergency care and are better served by professionals who are knowledgeable about their unique needs. Within emergency medicine, this is highlighted by the relatively recent formation of the Society for Academic Emergency Medicine Oncologic Emergencies Interest Group and the Comprehensive Oncologic Emergencies Research Network (CONCERN). Patients often relate stories of being told in their local emergency department (ED) to go to their cancer center for further treatment after emergent conditions have been excluded. Conversely, oncologists rarely have access to EDs with specific oncologic expertise. Patients express concern that emergency physicians in the community are not completely comfortable caring for complex oncologic patients and lack adequate knowledge regarding the management of their disease processes and treatments. As a result of their patients' prior experiences in these less specialized settings, oncologists are often hesitant to recommend such EDs with limited oncologic expertise to their patients. Many oncologists who work in large centers are requesting urgent and emergent after-hours services by personnel who are trained in handling oncologic emergencies. With overcrowding and prolonged waits for treatment that characterize many of our nation's EDs, those with cancer and complex care needs, including immunocompromised, intractable pain, and end-of-life care needs, may best be served in regionalized EDs specializing in oncologic care.

The numbers of cancer patients and survivors among the general population are increasing. The life expectancy of cancer patients has increased significantly in the last six decades. In 2017, there were an estimated 15,760,939 persons living with cancer in the United States alone. In 2020, an estimated 1.8 million additional Americans will be diagnosed with cancer. The 5-year survival rate was estimated to be 67.4% between 2010 and 2016 [1]. With the advent of new therapies and treatment modalities, this survival rate could conceivably increase.

Comparative survival data from the MD Anderson Cancer Registry (The University of Texas MD Anderson Cancer Center, Houston), established in 1944, demonstrate a marked improvement in survival rates for most malignancies. Examples include breast cancer, the 10-year overall survival rate having increased from 25% in 1944 to 76.5% in 1995 for patients treated at MD Anderson. For prostate cancer, the most common malignancy in men, the 10-year survival rate increased from 8.5% in 1944 to 82.5% in 1995. Acute myeloid leukemia was simply fatal in 1944, with a median survival from diagnosis of 8 weeks and a 99% mortality rate at 12 months, but by 2004, the long-term survival rate had increased to over 25%. Remission rates in acute myeloid leukemia patients under age 60 years have reached 65% [2]. Thus, there are many cancer survivors seeking medical care in primary care offices and EDs around the country.

To further highlight the need for such specialized care, there will be an estimated 26 million persons in the United States who either have active cancer or who have been previously diagnosed with cancer in 2040 [3]. Seventy-three percent of this population will be over the age of 65. This ever-growing and aging population will continue to seek emergency care both during and following the diagnosis and treatment of their cancer. Currently, about 4% of all ED visits are made by patients with a cancer diagnosis [4]. This population has a high rate of admission, 59%, when compared to the 16% admission rate for those without cancer [3]. This stems from infection, therapy side effects, manifestations of the malignancy itself, as well as a plethora of hematologic and metabolic derangements. With increasing prevalence, 5-year survival rate, and age of the patient, there

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will be an increasing need to have providers more familiar with cancer and its therapy. This may be best accomplished by personnel with additional experience and training in treating and managing this population.

Several other factors have increased the population of oncologic patients and survivors seeking acute care. In the last few years, more oncologic patients have been receiving treatment as outpatients. Leukemia and stem cell transplant patients spend less time in the hospital and often receive the majority of their chemotherapy in outpatient treatment centers. These patients are no longer universally admitted to the hospital for neutropenia if there is no evidence of infection. Instead, they make frequent trips to the hospital for treatment and laboratory evaluations. Often, patients arrange temporary housing in the area of the oncologic treatment center. This practice has also increased the need for unscheduled acute care. Furthermore, cancer patients and survivors have a combination of medical problems that may or may not be related to their cancer history and a wide range of potential residual medical issues related to their prior disease and/or treatments. Meanwhile, oncologic care is becoming increasingly specialized. Oncologic practice is focusing on emerging treatments and targeted therapies. As more treatment options become available, more expertise is needed in each oncologic subspecialty. With increasing treatment options, there are more potential side effects and treatments available for the supportive care of these patients.

Cancer patients not only suffer from complex medical problems related to their disease and therapy but also are particularly vulnerable emotionally. Patients suffering from a life-threatening illness often have stronger bonds with their medical providers that may be associated with higher expectations for care and an increased sensitivity to their care providers' words or actions; conversations can take on a greater meaning and become more emotionally charged than under normal circumstances [5].

Caring for patients with advanced cancer is stressful for clinicians, and discussing bad news often evokes strong emotional feelings. Not all physicians are formally trained for these difficult communication tasks. End-of-life talks are time-consuming and stressful in any environment, but this is compounded in the ED, where the cancer patient's needs must compete with the treatment demands of other patients. Furthermore, delirium may be far more common in this population than previously thought, which may prevent meaningful discussions in the ED [6]. Unfortunately, evaluation in the ED often reveals progression of the underlying malignancy and may raise the topic of transition to palliative care. Most emergency physicians feel ill-equipped to have this discussion due to the brief nature of their relationship with the patient and lack of depth of understanding of the patient's disease and its progression and possible therapeutic options. At the same time, the patient, faced with new knowledge about disease progression manifested by the symptoms that prompted the emergency visit, may have multiple questions and a high level of anxiety. At this time, the patient is at high risk for feelings of abandonment, especially if the emergency physician is unable to answer questions or provide adequate reassurance that the patient's primary oncologist will be available to them in a timely fashion [5]. Nursing staff may also be unprepared to care for patients who are actively dying, and they may lack the skills to manage end-of-life symptoms.

Despite these needs, there are very few acute care facilities dedicated entirely to the care of cancer patients. MD Anderson and Memorial Sloan Kettering Cancer Center (New York) have such centers. The Ohio State University Wexner Medical Center has an integrated Oncologic Pod within its main ED. Other institutions with a large percentage of oncologic patients are developing resources to provide the specialized care these patients need and to mitigate the difficulties these patients can present to a busy ED. Some institutions are opening fully integrated cancer units within their EDs. They are examining ways to quickly recognize acutely ill oncologic patients so that high-risk patients are treated expeditiously while maintaining an appropriate triage system so that other patients do not perceive oncologic patients as receiving preferential treatment [7].

In this chapter, we describe several models for providing care for oncologic patients in the emergency setting. The models range from EDs at large, dedicated cancer centers (MD Anderson and Memorial Sloan Kettering) to a fully integrated Oncologic Pod that resides within a more traditional ED (The Ohio State University Wexner Medical Center, Columbus, Ohio). These models illustrate some of the pivotal issues of institutions embarking on this endeavor.

Table 2.1 Common issues essential to all oncologic ED models

Recognition and expeditious treatment of oncologic emergencies such as neutropenic fever, spinal cord compression, tumor lysis syndrome, and pulmonary embolism
Appropriate management of pain for patients who are not opioid naïve
Management of frequently needed procedures such as thoracentesis and paracentesis
Early recognition and proper management of patients who have do not resuscitate (DNR) orders or are near the end of life
Knowledgeable management of complications of cancer treatment (chemotherapy, immunotherapy, radiation, CAR-T, and other novel therapies)
Proper communication regarding disease progression with the patient and oncologist
Adequate support from end-of-life services such as palliative care and hospice
Consistent and reliable method of communication with the patients' oncologists
Support for patients who are new to the institution and attracted by the cancer ED designation

Table 2.1 lists common issues that are considered essential to all models of care. Different models for providing emergency care to cancer patients are derived from the variable needs and characteristics of each practice, such as the prevalence of cancer types, the physical and administrative organization of the local oncologic services, and the resources available.

The University of Texas MD Anderson Cancer Center

The Emergency Center at MD Anderson Cancer Center is dedicated exclusively to the care of cancer patients. It is located in the main hospital building and is designated a level III ED by the The Joint Commission and the Centers for Medicare & Medicaid Services. Ninety-eight percent of patients treated in MD Anderson's ED have cancer or a cancer history. The ED has a large role in the inpatient services provided at MD Anderson. Thirty-nine percent of hospital admissions come through the ED [8].

However, MD Anderson did not open its doors with an ED in place. The ED developed gradually as a response to the needs for acute care for the large number of outpatients being treated at MD Anderson. Initially, urgent and emergent services were provided in an open ward. No doctors were assigned to the area, and when a patient requiring emergent care arrived, the patient's physician was notified and sent to the ward to evaluate the patient. This situation was not optimal for acutely ill patients or for patients scheduled in the clinic, and the lack of individual patient rooms made it difficult to maintain patients' privacy and confidentiality [9]. The system was also disruptive for oncologists, who already had full clinical schedules. Eventually, full-time physician coverage was established, initially provided by the Department of General Internal Medicine. In 1986, the ED was formally opened. Initially, it had 23 private rooms and provided care to approximately 14,000 patients per year. In 2007, the emergency center moved to its current expanded location. In 2011, MD Anderson established an academic Department of Emergency Medicine, the first such department dedicated entirely to oncologic emergency medical care, education, and research. The MD Anderson ED currently has 45 private rooms, a six-chair unit, and a two-chair triage bay. The ED is equipped with two resuscitation rooms in which critical care is provided to patients with high acuity that arrive from the clinics, walk-in, or arrive by ambulance. The ED now sees over 26,000 patient visits annually. All of the patients have cancer or are cancer survivors, except for an occasional family member of a patient or an employee.

The ED is staffed with full-time faculty members, the majority of whom are board certified in internal medicine or emergency medicine. Some faculty members are board certified in surgery, pediatrics, or infectious disease or palliative medicine. The physicians are faculty at the University of Texas and have similar academic obligations for research, administration, and teaching as other MD Anderson faculty members. The Department of Emergency Medicine recently initiated an oncologic emergency medicine fellowship, now in its eighth year. Mid-level providers are utilized in the ED, but provide a relatively small portion of the care delivered.

The department's 19 faculty members provide round-the-clock coverage. Coverage ranges from two to six physicians with an additional mid-level provider at the busiest times. The ED employs approximately 75 registered nurses with a nurse-to-patient ratio of approximately 1 to 3.

Care and treatment decisions are made by the emergency medicine faculty. However, oncologists do provide a call schedule, and there is frequent communication on an as-needed basis between the emergency physicians and primary oncologists. Oncologists do not routinely round in the ED unless they have admitted patients boarding there. The electronic medical record provides full access to the patient's medical record. Oncologists can notify the ED staff of a patient's pending arrival with the addition of important clinical information by entering a note in the medical record. After patients are seen, a note is generated by the emergency physician notifying the primary oncologist that the patient was seen. If consultation is warranted, the oncologist is contacted by phone.

The average ED length of stay is just over 6 h for a non-admitted patient and over 9 h for an admitted patient. The ED admits 51% of the patients presenting for treatment. Approximately 30% of unique patients have hematologic tumors (leukemia or lymphoma) or have received stem cell transplantation, comprising 50.3% of all patient visits; the remainder have solid tumors [7].

Of all the patients visiting the ED in 2010, hematologic patients averaged 2.2 visits per patient, and solid tumor patients averaged 1.8. Of these patients, 12% had four visits or more, with a range of 1–31 visits per patient. Most patients were receiving multiple medications and presented with several complaints. The complexity of their illness and frequent requirements for intravenous fluids, antibiotics, electrolytes, and blood products results in a prolonged length of stay compared to other EDs. The high level of acuity is reflected in the 10.9% mortality rate associated with admission of these patients [7]. The mortality rate is higher for patients with hematologic tumors (13.6%) than for patients with solid tumors (9.8%).

Patients present to the oncologic ED with a multitude of different complaints. At MD Anderson, the most common chief complaint is fever, present in 23% of patients. This is closely followed by abdominal pain, generalized pain, shortness of breath, nausea and vomiting, weakness and fatigue, back pain, chest pain, bleeding, cough, and diarrhea.

Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering has an Urgent Care Center (UCC), dedicated solely to the care of oncologic patients. The number of patient encounters per year in the UCC has steadily increased from 14,800 in 2000 to 21,800 in 2013. Although the UCC receives Memorial patients who arrive from the community via ambulance, general 911 calls from the community are not brought to Memorial. The physical size of the unit has grown over time. Originally an eight-bed unit with an adjunct clinic space, the UCC now consists of 19 telemetry beds and 4 transfusion chairs. Turnover of these beds occurs more than four times per day.

The driving forces behind this growth are an increase in the number of patients receiving treatment at Memorial Sloan Kettering and the continued transition of oncologic care away from the inpatient setting. As cancer treatment paradigms change, the UCC is key to the institution's ability to provide acute evaluation and management to an increasingly large and complicated outpatient population. The recent addition of a freestanding same-day surgical center and the continued expansion of the outpatient bone marrow transplantation program are examples of the trend toward outpatient treatment of cancer patients.

The clinical staff consists of 13 full-time board-certified internal medicine physicians, some of whom have completed subspecialty training in palliative care, anesthesia/critical care, and infectious disease. UCC physicians are considered academic faculty who are responsible for teaching medical students and residents from Weill Cornell Medical College, as well as participating in clinical research.

Patients treated in the UCC reflect the spectrum of disease seen at Memorial. Most patients have solid tumors (72%) and are evaluated for acute complications of their disease and treatment. The most common chief complaints include dyspnea (17%), fever (14%), pain (11%), nausea (10%), and fluid/electrolyte disturbances (9%). The average length of stay in the UCC is 4 h, and slightly more than half of the patients seen in the UCC will require admission to the hospital. Occasionally, patients with advanced disease who have been treated at other institutions or individuals with a suspected but unconfirmed cancer diagnosis seek to transfer their care by visiting the UCC. Emergent problems are acutely managed; however, referral for expedited outpatient evaluation is the preferred pathway, as the UCC is not intended to be the first point of contact for a new patient.

The UCC has attempted to integrate successful models of care from emergency medicine as volume and throughput have increased. A modified Emergency Severity Index (ESI) tool is used for triage. Patients are assigned a score of 1–5 based on the need for a lifesaving intervention, the presence of a high-risk situation, the number of resources a patient will require, and predefined vital signs. Specific triaging emphases that reflect the unit's focus on oncologic include with the rapid identification any of the following conditions: recent bone marrow transplantation, febrile neutropenia, and potential spinal cord compression. During peak hours, a UCC physician assists the triage nurse, a model that has been associated with faster throughput and improved patient outcomes in non-cancer EDs [10].

As many patients are referred internally by treating oncologists and surgeons, an electronic "UCC Notification Order" allows these individuals to communicate the most likely diagnosis, the need for admission, and which tests and consultants will expedite care.

Oncologic patients have an inherent risk for developing sepsis. An institutionally derived algorithm is used to screen all electronically documented vital signs for sepsis. When potentially significant abnormalities are identified, an alert is triggered, prompting a clinician to assess the patient for the possibility of sepsis. This process is time sensitive and requires the clinician to either document a reason for exclusion (dehydration, arrhythmia, end-of-life/palliative care, etc.) or acknowledge the alert and initiate the sepsis management protocol within 30 min.

Patients who arrive critically ill and in need of an immediate intervention such as endotracheal intubation, cardiopulmonary resuscitation, or initiation of vasopressor support are frequent challenges in cancer EDs. At Memorial Sloan Kettering, the primary oncologist has often already established and documented the goals of care in the electronic medical record. If the patient has previously consented to a do not resuscitate (DNR) order, this information is displayed in the header at the top of the screen, next to the patient's name and medical record number. This order must be confirmed and renewed with each hospitalization, as per New York State law. For critically ill patients without previously established advanced directives, the UCC clinician will rapidly determine the goals of care with the patient, healthcare proxy, and primary physician at MSK. For individuals who decline life-sustaining interventions, the UCC clinician will enter a DNR order and initiate palliative care. Preexisting order sets for narcotic analgesia and a palliative care consultant facilitate care. A medical ethics consultation service is available 24 h a day for encounters in which the goals of care are difficult to establish.

A Fast-Track Pathway is used for patients with a low Emergency Severity Index (ESI) score. One of the most common diagnoses in this group is a new, suspected, or incidentally identified thromboembolic disease. If anticoagulation is indicated, the patient is often discharged on rivaroxaban with close follow-up in the Anticoagulation Management Clinic.

In July 2013, the UCC opened an observation unit, intended for patients who were unsuitable for discharge but had an expected duration of care lasting less than 24 h. Although the observation unit is physically located in the hospital, this nine-bed unit is considered an outpatient service and is staffed by UCC physicians and mid-level provid-

ers. During the first 6 months of the program, roughly 10% of UCC visits ($n = 1013$) resulted in patient placement in the observation unit. The proportion of admissions to the hospital from the UCC with a length of stay less than 24 h dropped significantly after observation unit implementation (2.4–1.1%). The most common reasons for observation unit placement are fluid and electrolyte disorders (14%), pain control (14%), dyspnea (13%), and fever (9%). Interventions for patients in the observation unit include placement or revision of drainage catheters (pleural, biliary, genitourinary tract, abscess); endoscopy and transfusion in patients with hemodynamically stable gastrointestinal bleeding; correction of uncomplicated electrolyte derangements; administration of intravenous (IV), antiemetics, IV antibiotics (for treatment of cellulitis, pneumonia, and uncomplicated febrile neutropenia), or IV analgesia; and the management of severe constipation. Approximately one-third of patients placed in the observation unit require admission to the hospital for ongoing care. Extending the observation period to 48 h may decrease this number.

Approximately 15 patients a week are seen in the UCC for elective palliative paracentesis, performed by the UCC clinical staff. Drainage of symptomatic pleural effusions is performed in the observation unit by pulmonary medicine. Patients with low-risk febrile neutropenia are either discharged or placed in the observation unit for 24 h.

When possible, management decisions are made with input from a patient's primary oncologist or surgeon, who is notified automatically by e-mail during check-in and discharge. While these individuals may be off-site, they are able to review all relevant clinical data, including lab findings, chart notes, and radiology and telemetry results. An electronic status board, visible on all computer terminals within the institution and on overhead monitors in the UCC, facilitates a quick grasp of key metrics related to an individual patient and overall throughput at any given time. This tool facilitates communication about arrival and waiting times, identification of treating or covering UCC staff, pending diagnostic tests and consultants, disposition (admitted/discharged/observed), and bed status.

The Ohio State University Comprehensive Cancer Center: Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

In April 2015, the Ohio State University Wexner Medical Center (OSUWMC) opened a new, specialized pod in the ED to care for its cancer population. The ED, which houses the newly named Oncologic Pod, currently cares for all patients that arrive to OSUWMC seeking emergency care: approximately 82,000 patients per year. The Oncologic Pod currently evaluates, manages, and treats approximately 11,000 oncologic and hematology patients per year, which reflects over 13% of emergency visits to the OSUWMC ED. With opening of the Oncologic Pod, the ED dealt with many challenges as illustrated in Table 2.2, beginning with patient identification. The hematology and oncologic patients are identified immediately upon arrival during the triage process. Patients who arrive to the ED are asked two screening questions: "Have you seen a cancer doctor or doctor at the James in the last 12 months?" and "Are you currently undergoing active treatment for cancer?". An affirmative answer to either question allows for preferential placement into the Oncologic Pod, which is fully integrated within the ED.

Table 2.2 Challenges to an integrated Oncologic Pod

Early identification of the hematology and oncologic patient
Equitable triage and placement for all ED patients
Identification of febrile neutropenia and other subtle, life-threatening oncologic emergencies
Waiting areas for the immunocompromised patient
Available bed space
High ESI level in the cancer population
High admission rate in the cancer population

One of the many challenges that the ED initially faced was the development of triage criteria to effectively triage cancer patients to the Oncologic Pod while maintaining equity among all patients that presented for evaluation. The Oncologic Pod originally opened with 10 beds and 5 additional chairs for a total of 15 treatment spaces that were allocated to the care of cancer patients. Ten of the rooms were private, four had private bathrooms, and two had negative airflow. The other five spaces were treatment bays with lounge chairs for infusions. With rising acuity and increasing number of cancer patients arriving to the ED, these treatment bays were renovated to include telemetry and actual ED beds, instead of the initially planned chairs. Additionally, the ability to flex up to 19 treatment spaces was created through the addition of four hallway beds. Patients may be placed in a hallway bed to facilitate early treatment while awaiting placement in a room or treatment bay. On days when a larger number of oncologic and hematology patient visit than the 15-bed/19-treatment space pod can accommodate, additional patients will be evaluated in the remainder of the ED when space is available. If a high acuity patient arrives to the ED and the Oncologic Pod is full, then that patient may be placed in a bed outside of the Oncologic Pod to facilitate prompt treatment of the emergent medical condition. Similarly, when there are fewer Oncologic Pod patients, non-cancer patients will be evaluated as needed in the Oncologic Pod. This will ensure equal access to emergency care for all patients, regardless of their disease state.

After the initial triage process, patients are either placed in an available treatment space or escorted to the waiting

room. The waiting room represented an additional challenge. With the steadily rising number of ED visits by cancer patients, concerns arose in placing what could certainly be an immunocompromised population in the main ED waiting room. The main ED population often sought care for viral or bacterial illnesses. Such illnesses could prove life threatening for the immunocompromised cancer patient. Out of concerns for patient safety, an additional waiting area for cancer patients was created that allowed for better isolation and distancing. The cancer population viewed this as a significant improvement in their ED encounters. Hand sanitizer and facial masks are readily available for patient use in this area.

After patients are placed into a treatment space, they are cared for by a multidisciplinary team in the Oncologic Pod. This team is composed of physicians, advanced practice providers, nurses, patient care associates, patient experience representatives, social workers, case management, and dedicated emergency medicine trained pharmacists. All physicians that care for these patients are either board certified in emergency medicine or board eligible for the American Board of Emergency Medicine certifying board exam. The physician group provides 24/7 oversight of the Oncologic Pod. There are 16 hours (two, 8-hour shifts) of dedicated physician coverage in the Oncologic Pod. This runs from 9 a.m. until 1 a.m. During this time period, the dedicated physician is responsible only for care in the Oncologic Pod. Additional physician staffing throughout the department enables this physician to dedicate all of their time on shift to the cancer population. From 1 a.m. until 9 a.m., an emergency physician provides oversight in the Oncologic Pod as well as an adjacent ED area. The decision for this staffing model was based on ED arrival times of the cancer population at the OSUWMC ED, which consistently demonstrated fewer arrivals in the 1 a.m. to 9 a.m. time period on all days of the week.

To assist the physician in caring for patients, a group of advanced practice providers (APPs) staff the Oncologic Pod. This group, a mixture of both nurse practitioners and physician assistants, is dedicated solely to the care of patients in the Oncologic Pod. The APP staff provide 48 hours of coverage daily in the Oncologic Pod. This is broken down into four, 12-hour shifts with overlapping coverage. During the onboarding process, the APP staff are cross-trained in the ED and the cancer center. This includes time in the Oncologic Pod as well as rotating with the hematology, oncologic, and neuro-oncologic services. Depending on provider preference, they may also spend time with radiation oncologic or one of the many surgical services for the hospital. The off-service onboarding process prepares the APP staff for the variety of cancers and treatments that they may encounter in their role as providers. Their time onboarding in the ED further prepares them for the variety of presentations that they may encounter in their role. The APP team evaluates the vast majority of patients in the Oncologic Pod. If there is an influx of patients, then resident physicians, who staff the adjacent pod, are readily available to assist in evaluating the cancer population. Additionally, they have 24/7 access to a board-certified emergency physician. Through the combination of onboarding, monthly meetings, CME, and personal education, the APP staff is more than adequately prepared to deal with any oncologic emergency that comes through the door.

The work of the providers would be naught without additional staff. The Oncologic Pod has a dedicated nursing staff. The vast majority have had training either in the care of the oncologic patient or in an ED. The nursing staff is acutely aware of the presence of ports and use of other intravascular access devices. They are attuned to the needs of this particular population including aggressive symptom control and need for expeditious evaluation of a fever. The nursing staff is aided by patient care associates, up to three at a time, who help with additional tasks in the area. To help complement the immediate patient care side, 24-hour social work is available for the patients. Every cancer patient who is roomed in the ED is evaluated by a social worker to discuss living situations, safety, and advanced directives. The social work team is readily available to assist the population around the clock. Case managers also help with coordination of care. They are available to connect the differing care teams as well as to establish appointments for patients being discharged from the Oncologic Pod. Finally, the Oncologic Pod has a dedicated pharmacist, trained in emergency pharmacology. They help with a variety of issues, including antibiotic selection, antibiotic dosing, symptom control, and any other pharmacotherapeutic questions the treatment team may have. They are a valuable resource as cancer treatments continue to evolve.

One important scenario to emphasize is the patient with neutropenic fever. These patients are often difficult, but critical, to recognize. Current guidelines recommend that these patients receive antibiotics within 1 hour of triage and be monitored for 4 hours following antibiotic administration [11]. Many of these patients may appear well and traditionally have had to wait with other patients for further evaluation. Unfortunately, a prolonged time to antibiotics can result in deterioration and development of sepsis. To improve the management of these patients, the Oncologic Pod has the criterion that any patient with a fever who has received chemotherapy or radiation in the prior 2 weeks will be evaluated under the ED Sepsis Alert process. This process brings together a multidisciplinary team (physicians, nursing, radiology, pharmacy, etc.) to expedite initiation of IV antibiotics and diagnostic work-up for this high-risk population of patients.

As treatments advance, there is the ongoing need for increasing flexibility in triage. With the FDA approval of CAR-T therapy, new challenges arose. For this reason, any

patient on CAR-T therapy in the James Cancer Center is provided with a card to present upon arrival to ANY ED. This details their therapy and possible side effects including complement release syndrome and neurologic side effects. The card also contains a number for outside hospitals to call for guidance on treatment. At the OSUWMC ED triage, a third screening question was recently added to help identify this population upon ED arrival. Other oncologic emergencies may be harder to identify. However, with the Oncologic Pod screening pod questions at triage, patients are immediately flagged as cancer patients upon arrival. This gives the Oncologic Pod physician and APPs, as well as the provider in triage, the opportunity to review the patient chart, chief complaint, and triage note. These providers are able to work with the triage nurses and charge nurses to expedite care of the cancer population including ordering CT scans, labs, or symptom control in triage. They can also increase or decrease the ESI or recommend that a certain patient get the next available treatment space if there is a concern for other subtle oncologic emergencies.

Other challenging scenarios that the Oncologic Pod has encountered include the arrival of patients without a clinical cancer diagnosis. An inpatient service was designed that handles the care for patients without a definite cancer diagnosis but identified as being at high risk for malignancy (i.e., new, large lung mass or abdominal mass). This facilitates the care of patients with a presumed diagnosis of cancer who may be attracted to the cancer ED, either based on outpatient imaging or as transfers from outside hospitals. This allows for patients who are not already receiving their cancer care at the James Cancer Center to be seen in the Oncologic Pod to facilitate transition of their care to the cancer center. Additionally, if patients do not require hospital admission for this work-up, a James Diagnostic Clinic can facilitate an expedited work-up for outpatients. The Oncologic Pod serves as the first point of contact of the James Cancer Center for one to two patients per day, so this is not an unusual scenario. While there is month-to-month fluctuation, this number has generally increased since the genesis of the Oncologic Pod in 2015.

As patient volumes rose over time, it became apparent that there was not only a growing need for emergent cancer care but also the need for acute, unscheduled visits. The acute, unscheduled visit encompassed patients who might need to see a provider, though do not necessarily need an ED encounter. This could range from fever in patients not on cytotoxic chemotherapies, anemia, thrombocytopenia, electrolyte abnormalities on routine labs that need follow-up, ED follow-up, or even clinic overflow when patients are not able to see their primary team. This necessitated the development of an additional eight-bed treatment space, the Immediate Care Clinic (ICC). The ICC is a 24/7 treatment space that opened in 2018. Patients established with the James Cancer Center, or in the process of establishing care, can be referred to the ICC by their provider, the ED, or the nursing triage line. Certain exclusion criteria were created to prevent those with true emergencies from arriving at the ICC. Such patients are redirected to the ED for emergent care. The ICC is staffed by the same APP group as the Oncologic Pod. It is overseen by the Oncologic Pod emergency physician. The ICC admission rate is consistently below 30%. It serves as an intermediary between the ED and outpatient worlds. This allows for lower acuity patients to be seen promptly when ED volumes are high and prevent unnecessary ED visits, increased charges to the patient, and increased overall healthcare costs.

It is one thing to establish an Oncologic Pod for cancer patients, and yet another to ensure that quality standards are being met. In order to assure that patient care is performed at the highest professional standards, there are regular evaluations of specific ED metrics. This occurs both at the level of the Department of Emergency Medicine and at the hospital level. A monthly scorecard containing information such as patient arrivals, door to provider, length of stay, admission rate, and new patient contacts is disseminated to the administration of both the hospital and ED. It is regularly reviewed by the Department of Emergency Medicine administration in conjunction with nursing leadership. It is also reviewed semiannually at the hospital level in forums such as the Patient Quality, Safety, and Reliability Committee and the Medical Staff Advisory Committee and with the Chief Medical Officer of the James Cancer Center. To ensure that patient voices are heard, patient experience representatives are available to speak with patients. Additionally, all patients who arrive are provided with a direct phone number to the patient experience representative line in the event they wish to express gratitude or concern about their ED stay. These accolades and concerns are reviewed and addressed on a weekly basis in a multidisciplinary meeting including patient experience, physician leadership, and nursing leadership. These measures ensure that high-quality care is being delivered to the patients and that all needs and expectations are met.

Current and Future Considerations for the Cancer Emergency Department

Increasing specialization has resulted in a fragmentation of medical care and cancer care is no exception. Many oncologic patients are treated by several physicians who are all specialists in cancer therapy. One patient may have one or more surgeons, a medical oncologist, a radiation oncologist, and a palliative care physician. This does not include other specialists for chronic issues or problems that develop during treatment, including cardiologists, nephrologists, endocrinologists, and pulmonologists. Patients are often confused as

to which doctor is "in charge" and whom to ask which question. The role of the emergency physician in a comprehensive cancer center has some similarities to that of a primary care physician. The ED physician often explains the roles of the different providers and facilitates communication between the various specialties involved in the patients' care. Another important role is that of a safety net, by providing care to the patients when they cannot wait for an office visit or when the office visit results in the discovery of a problem that is beyond the scope of the oncologist or specialist. In these roles, the ED supports both oncologists and patients. Physicians specializing in oncologic emergencies use unique skills and knowledge of potentially dangerous complications of different treatment modalities and the best supportive therapies as well as understanding of the disease process of multiple different malignancies and their associated emergencies. Also valuable are expertise in pain management, procedures commonly needed in cancer patients, and skillful management of palliative and end-of-life care. This skill set, which currently can only be obtained through experience, helps doctors who specialize in the acute care of cancer patients make decisions regarding the aggressive or supportive nature of care provided in the cancer ED.

Several themes are prevalent in the acute care of cancer patients. One of the concerns expressed by physicians seeking to provide acute care to oncologic patients is access to the complete medical record and the expertise of the oncologist. The ED physicians must have a significant understanding of the treatment paths and modalities of the patients they are seeing. In order to make appropriate decisions, communication must be available with the oncologist and other supportive services. With more knowledge and experience, the emergency physician can be more effective in support of the patients and the oncologists and be more confident in their independent decision-making. A method of documentation and a process of communication that make the primary oncologist aware of all visits to the ED are optimal. At MD Anderson, an online medical record documents the visit and outcome, and is accompanied by an e-mail notifying the oncologist of the emergency visit, closing the communication loop. Memorial Sloan Kettering has gone one step further by posting the ED tracking board throughout the institution. At the The Ohio State University Wexner Medical Center, oncologic teams are notified of emergent visits by e-mail. They are also available to discuss patient care in real time through a variety of modalities.

Another common concern is that caring for this group of patients is very labor intensive. These patients are often very ill; many of them are not independently ambulatory. Most of the patients are on multiple medications and have numerous comorbidities and several complaints. Due to the complexity of their illness, their stay in the ED is longer than that of other populations. Many of the patients require electrolytes or blood replacement as an incidental finding or the reason for the visit. These processes add to the time in the ED and the nursing workload. The ubiquitous admission rate of over 50% and the high mortality rate of patients admitted through the ED are further testimony to the high acuity level of the patients [3].

An ED that treats only cancer patients does not have to devise a triage method to identify the cancer patients from the non-cancer patients, and recognition of neutropenic fever, sepsis, and infection with underlying immunocompromised is routine. Other problems, such as managing intractable pain and mixing and adjusting large doses of opioids, are a frequent occurrence. However, these are issues that EDs—who want to support a large cancer population but cannot be dedicated solely to that population—contend with. A frequent issue more unique to a cancer ED is the arrival of patients with a recent diagnosis of suspected or confirmed malignancy. One of the challenges of working in a cancer ED is handling a group of patients with varying degrees of illness, varying knowledge about their condition, and different stages of diagnosis who have recently received difficult news and are emotionally charged. In all of the functioning cancer EDs interviewed, avoiding having the cancer ED serve as the intake portal for the cancer institute has been a common theme. Another frequent challenge is patients with late-stage cancer with no prior relationship to the parent institution. Many of these patients have received treatment at other centers and when told that no further treatment options exist, go to the cancer ED hoping for a salvation therapy. These patients are often too sick to be discharged and, without the evaluation of an oncologist in the emergency center, will ultimately be admitted to the hospital for an expert opinion and transition to supportive care or hospice. A consulting service that is available to see such patients in the ED would make this process more satisfactory.

Therapeutic procedures frequently utilized in cancer patients necessitate the development of certain services. Oncologic patients have a frequent need for invasive procedures such as thoracentesis, paracentesis, stenting, and percutaneous drainage. Some of these procedures can be done by ED physicians, but they are time-consuming and difficult to perform in a busy ED. Several institutions have dedicated teams to help facilitate these procedures. Another common diagnosis is the incidental finding of pulmonary embolus on CT scans. Many of these patients are handled in the emergency centers at Memorial Sloan Kettering, MD Anderson, and OSUWMC.

The optimal medical management of many cancer-related emergencies is an excellent area for further research. Many practice patterns are based on expert opinion or prior experience rather than clinical trials. Formal training for treatment of oncologic emergencies is still up and coming, though models do exist [12]. Otherwise, this skill set currently must be learned through work experience. Examples of frequently treated problems that could be better supported by research are treatment of hyponatremia and hypercalcemia of malignancy, rescue treatment of chemotherapy- or radiation-induced nausea and vomiting, chemotherapy- or radiation-induced diarrhea and mucositis, chemotherapy-induced peripheral neuropathic pain, pain related to colony-stimulating growth factors, dosage of steroids and radiation in malignant spinal cord compression, and acute management of narcotic-induced constipation. Other important areas include treatment of therapy-associated skin rashes and management of medical problems with unique complications, such as venous thromboembolism and acute coronary syndrome in thrombocytopenic patients and anticoagulation of patients who have metastatic disease to the brain.

In summary, the care model used for patients with oncologic emergencies must be tailored to the local medical and oncologic environment; therefore, it naturally follows that different medical systems have developed different processes to care for these patients. A constant among the models discussed here is the underlying goal of care being provided to these patients by clinicians who are knowledgeable about their needs and have integrated communication with the primary oncologists. Acute care of the oncologic patient is gaining recognition as an important area that could be improved upon with increased training, research, and emphasis on integration into the oncologic system.

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Informatics

3

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Introduction

Clinical informatics is the study of information technology as it applies to clinical care within the health system. The American Medical Informatics Association (AMIA) considers informatics when used for healthcare delivery to be essentially the same regardless of the health professional group involved. *Clinical informatics* is concerned with information use in healthcare by clinicians. Clinical informatics includes a wide range of topics ranging from clinical decision support (CDS) to visual images; from clinical documentation to provider order entry systems; and from system design to system implementation and adoption [1]. In this chapter, our goal is to introduce the reader to new and old concepts that will allow the user to assess information and knowledge to meet the needs of healthcare professionals and patients. The reader will be able to characterize and evaluate information technology, so that they are better able to refine clinical workflow processes, develop new processes, implement those processes, and refine clinical decision support systems [2]. Knowledge of these elements will aid providers in clinical care to their patients. We will discuss workflow, clinical decision support, information technology systems, and communication, concluding with a discussion of cancer registries and research.

Workflow Process Redesign and Quality Improvement

Workflow has been studied both as a concept and a phenomenon. As a concept, workflow is defined as the sequence of physical and mental tasks performed by people within and between work environments. The flow of information, objects, and people using information and objects through space and time represents the phenomena of workflow. Clinical workflow studies aim to model a simplified version of work in the complex healthcare setting [3]. The simplification achieved by modeling aids in making complex systems more comprehensible as a result of the explanatory nature of such models [4, 5].

Multilevel perspectives are useful to understand workflow comprehensively in the complex system of healthcare [6]. Workflow can occur sequentially or simultaneously and at various levels (individual or organization). Workflow occurs interorganizationally, between clinic employees, and for individual employees before, during, and after a patient encounter. Cognitive workflow occurs as cerebral processes in collecting data and making decisions.

An example of workflow can be illustrated in the ordering of a medication. The workflow of ordering a medication includes communication between the provider and the patient, the provider's mental processes, and the physical action by the provider of writing the prescription on paper or electronically into an electronic health record and sending the order electronically or the patient taking the paper prescription to the pharmacy. In this example, one can see the use of cognitive, individual, organizational, and intraorganizational workflow.

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Any time there is a change in practice, particularly related to health information technology, workflow changes occur. Delays in patient care, billing, and communication are prone to occur if the workflow is unaccounted for, overlooked, or oversimplified. All healthcare organizations, regardless of size, must identify a person or group to monitor and assess current and anticipated workflow. Workflow information should be collected as early as possible, ideally before implementing a health IT system, and continually assessed including post implementation as a form of continuous process improvement.

Workflow Analysis

Workflow analysis may be used to improve the outcome of healthcare processes and products, including the practice of healthcare informatics. Institute of Medicine landmark reports call for the use of workflow analysis in an effort to improve healthcare quality, efficiency, effectiveness, and safety [7]. Analysis of workflow requires a reduction of a complex process into analyzable parts in a stepwise fashion.

Various tools can be used during workflow analysis, and a single approach will likely capture a small subset of the complexity. Methods to capture workflow data include qualitative, quantitative, and mixed methods [8]. Qualitative methods focus on naturalistic observation of subjects and activities using artifact collection, spatial analysis, and interviews. Quantitative methods are a more structured approach. Time-motion studies can track the efficiency and quality of healthcare workflow, quantifying the time involved in tasks by observation, self-reporting, or automation to collect temporal data [9]. Questionnaires and surveys are also used as workflow analysis methods. Data collected from the electronic medical record including audit logs, a form of metadata, is a new and emerging area of data collection for workflow methodology.

Visualizing workflow is an important tool as it provides users with cognitive support for visualizing detailed processes, showing parallel processes and allowing different perceptions of processes [10]. The most common method of visualization is flowcharting (process mapping). Flowcharting shows how processes really happen, rather than how they are expected or supposed to happen. This method helps one understand what contributes to different types of flows for the same process, find ways to improve the flows, and identify ways that health IT will affect workflows. Flowcharting is accomplished in five general steps: (1) decide on the process to examine; (2) create a preliminary flowchart; (3) add detail to the flowchart; (4) determine who needs to be observed and interviewed; and (5) do the observations and interviews [11]. An example of a flowchart from a patient being diagnosed with cancer and undergoing treatment and follow-up is shown in Fig. 3.1.

Workflow Redesign

The goal of workflow redesign is to create workflow that supports improved outcome of workflow activities (patient care). Workflow reengineering requires deliberate steps including changes to the mental and physical steps of people who move through a workflow process and changes to the steps in the interactions among organizations involved in a process. Karsh and Alper suggested a system to ten steps of process redesign as seen in Table 3.1 [12]. Broadly, process redesign is achieved by assessing the current state, envisioning the desired future state, planning to get to the future state, carrying it out, and evaluating the outcome.

Quality Improvement

Quality improvement in healthcare is a continuous method for improving process performance. Several quality improvement methodologies are used in healthcare. The Plan-Do-Study-Act (PDSA) is a prominent method that leads quality improvement cycles. The "plan" phase includes identifying a problem and potential solutions. "Do" involves a polar testing of a solution. The "study" phase evaluates if the change was successful. "Act" involves adopting, adjusting, or abandoning the implemented solution. Lean is another process improvement strategy that emphasizes value to customers by utilizing root cause analysis to eliminate waste and improve process flow. Six Sigma is another process improvement methodology that emphasizes quantitative and statistical approaches in continuous quality improvement at the project level to reduce process variations and eliminate defects.

Conclusion

Workflow is the sequence of tasks performed by various people within and between work environments. Workflow analysis is an integral part of quality improvement implementation and health informatics. In this chapter, we have outlined workflow analysis tools, a framework for workflow redesign, and gave an overview of quality improvement methodologies.

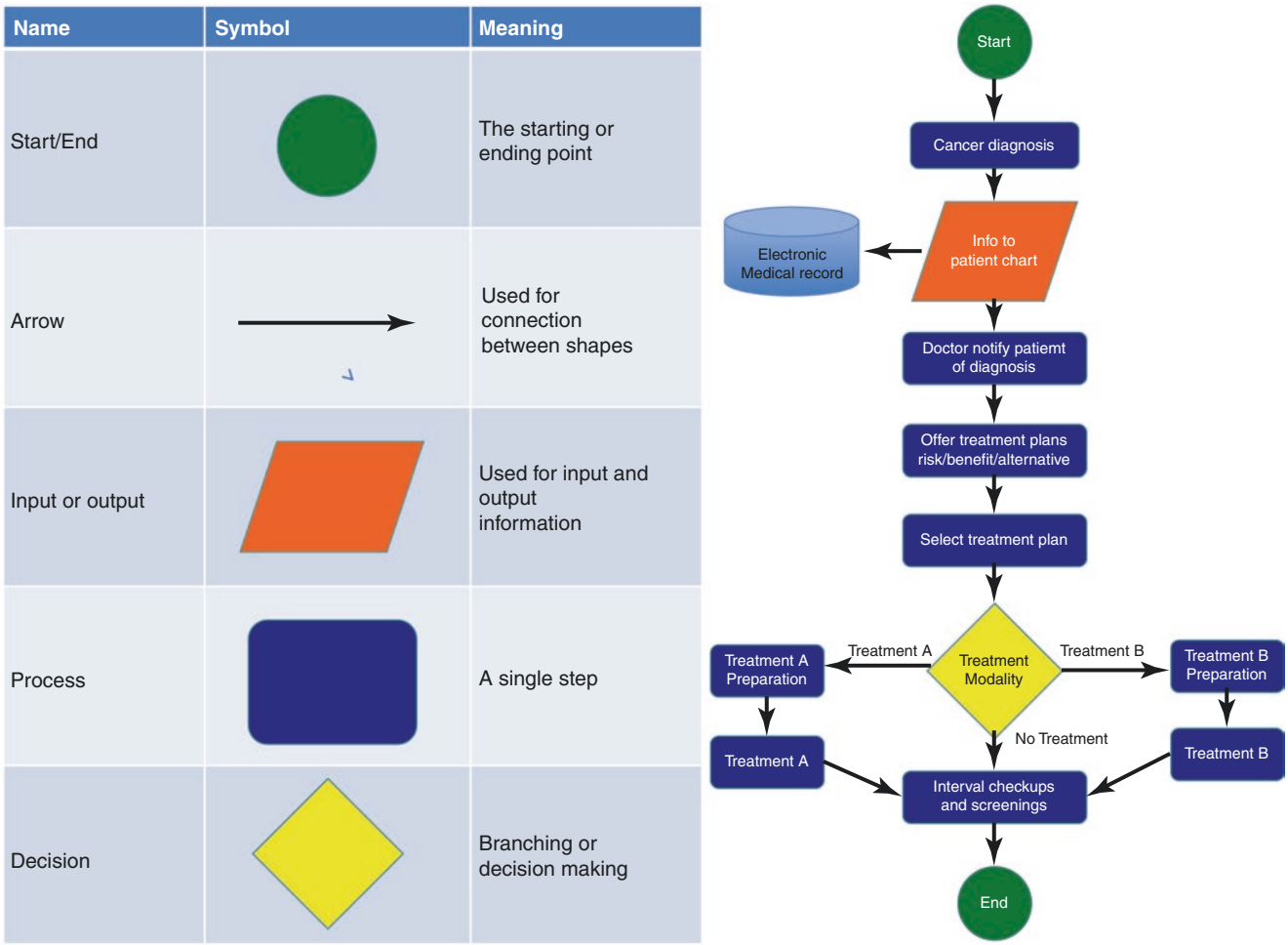

Fig. 3.1 Example flowchart of a patient being diagnosed with cancer, undergoing treatment and follow-up

Table 3.1 Karsh and Alper's ten steps of process redesign [12]

Ten steps of process redesign	
Step 1	Decide what system will be the subject of analysis
Step 2	Produce a preliminary work system map
Step 3	Use the preliminary workflow map to determine who should be represented on the team that will carry out the analysis
Step 4	Conduct an initial scan of the system with the team
Step 5	Determine boundaries of the system under study
Step 6	Determine performance expectations for each step in the system
Step 7	Begin formal data collection to review and update the workflow map. Gauge the current performance of the system, and determine baseline measures that will be used to evaluate the effectiveness of the redesign
Step 8	Analyze the data
Step 9	Once hazards (i.e., causes of failure modes or variance) have been identified, control strategies should be developed
Step 10	Analyze redesign ideas. Decide on a redesign idea, pilot testing, and implementation

Clinical Decision Support

The Office of the National Coordinator for Health Information Technology (ONC) defines clinical decision support (CDS) as providing clinicians, staff, patients, or other individuals with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and healthcare [13]. CDS are set of tools and logic to assist providers in making uncertain decisions. All medical decisions come with some percentage of uncertainty: diagnosis, testing, natural progression of disease process, treatment, and subsequent effects. CDS has evolved to remove some of the cognitive burden involved in medical decision-making.

There are some fundamental concepts we will review in order to leverage additional tools to aid in CDS. The first is the concept of expected value and expected utility. *Expected value*

(mathematical expectation, mean or average) is the random variable in a simplification of the weighted average and intuitively is the arithmetic mean of many independent realizations of that variable [14], whereas *expected utility* concerns people's preferences about choices that have uncertain outcomes (gambles). The expected utility states that the subjective value associated with an individual's gamble is the statistical expectation of that individual's valuations of the outcomes of that gamble, where these valuations may differ from the dollar value of those outcomes [15]. *Expected utility theory* is a theoretical approach to making optimal decisions under risk [16].

An example of these two concepts: in the presence of risky outcomes, a decision-maker does not always choose the option with higher expected value investment. Suppose there is a choice between a guaranteed payment of $1.00 and a gamble in which the probability of getting a $100 payment is 1 in 80 chances and the alternative, far more likely outcome (79 out of 80) is receiving $0. The expected value of the first alternative is $1.00 and the expected value of the second alternative is $1.25. According to expected value, people should choose the $100-or-nothing gamble; however, as stressed by expected utility, some people are risk averse enough to prefer the sure thing, despite its lower expected value. People with less risk aversion would choose the riskier, higher-expected-value gamble [15].

Expected value of gambling:

- If you gamble and win, you get $100.00.
- If you gamble and lose, you get nothing ($0.00).
- If you don't gamble, you are guaranteed $1.00.

$$\text{Formula}: \$100 * \left(\frac{1}{80}\right) + \$0 * \left(\frac{79}{80}\right) = \$1.25$$

Similar to engineering as it relates to healthcare, diagnostic inferences models have two elements: *tests* and *conclusions. Tests* include any source of information that can be used to determine the health of a system. *Conclusions* typically represent faults, including hardware fault modes, functional failures, specific non-hardware failures, and specific multiple failures. A conclusion may also indicate the absence of a failure indication (no fault). With this model, one can revise and refine opinions with imperfect information, comparable to a differential diagnosis. There are three characteristics to consider in making a diagnosis: detection, localization, and isolation, as defined in Table 3.2. In developing a diagnosis, the reader should focus on concepts emphasizing a structured approach to system testing and diagnosis. These include:

Table 3.2 Characteristics considered when making diagnoses

Characteristics	Definition
Detection	The ability of a diagnostic strategy to identify that a failure in some system has occurred
Localization	The ability to say that a fault has been restricted to some subset of the possible causes
Isolation	The identification of a specific fault through some test, combination of tests, or diagnostic strategy

- Maximizing reuse of design and test data, information, knowledge, and software
- Integrating support equipment and manual testing, to provide complete coverage of diagnostic requirements
- Integrating available diagnostic information, to minimize required resources and optimize performance

Capturing the relationships between tests and diagnosis provides a knowledge representation that can be processed by a reasoning system for health management. Initially, equal quality among test results is assumed and that every test outcome reflects the state of the unit being tested. In practice, this assumption is often relaxed to allow a measure of confidence to be associated with each test [17, 18].

Concepts of CDS include *heuristics*, which are patterns of bias in CDS. Heuristics is any approach to problem solving that employs a practical method that is not guaranteed to be optimal, perfect, or rational, but is nevertheless sufficient for reaching an immediate, short-term goal. Heuristics can be mental shortcuts that ease the cognitive load of making a decision [19]. Heuristics are the strategies derived from previous experiences with similar problems. These strategies depend on using readily accessible, though loosely applicable, information to control problem solving in people, machines, and abstract issues [20]. Some of the more common heuristics that apply to healthcare can be seen in Table 3.3 [21–27].

Cost-effectiveness analysis is a form of analysis that compares the relative costs and outcomes (effects) of different courses of action. Cost-effectiveness analysis is distinct from cost-benefit analysis, which assigns a value to the measure of effect. Typically, the cost-effectiveness analysis is expressed in terms of a ratio where the denominator is a gain in health from a measure (years of life, sight-years gained) and the numerator is the cost associated with the health gain. Cost-utility analysis can be used in decision analysis to define the "value" of an outcome node by adjusting the value of the outcome based on the perceived utility of that outcome for the patient. The most familiar outcome measurement is quality-adjusted life years (QALY) [28].

Table 3.3 Common heuristics in healthcare

Heuristics	Definition	Example
Availability	Overestimating the probability of unusual events because of recent or memorable instances [21]	*The last patient I saw with symptom X had disease Y, so we should test for Y*
Representativeness	Overestimating of a rare disease by matching patients to "typical picture" of that disease [22]	*He has features of the rare disease X, so we should test for it*
Anchoring	The failure to adjust probability of a disease or outcome based on new information, like "premature closure" [23]	*I was told in sign out that he had condition X, so I didn't consider it might be condition Y, despite lab results*
Value-induced bias	Overestimating the probability of an outcome based on value associated with that outcome [24]	*It would be horrible to miss a brain tumor in this patient with new onset headache, so we should get a head CT*
Affect heuristic	A mental shortcut that uses emotion to influence the decision. Emotion is the affect that plays the lead role that makes the decision or solves the problem quickly or efficiently. It may be used while judging the risks and benefits of something [25]	Your "gut decision" about the presentation of a patient
Familiarity heuristic	A mental shortcut applied to various situations in which individuals assume that the circumstances underlying the past behavior still hold true for the present situation and that the past behavior thus can be correctly applied to the new situation [26]	*I am familiar and comfortable with the Arrow Triple Lumen kit by Teleflex; I now need an arterial line kit, so I will choose the Teleflex brand since I am familiar with their other products*
Simulation heuristic	A simplified mental shortcut in which people determine the likelihood of an event happening based on how easy it is to mentally picture the event happening [27]	When the provider can easily "mentally undo" the sequence of events that led to a specific outcome like the placement of a chest tube or a cardiac arrest resuscitation

So, what makes a good test? Most would say a test with a high sensitivity and high specificity. Sensitivity is the measure of the proportion of actual positives that are correctly identified. Specificity is the measure of the proportion of actual negatives that are correctly identified. Sensitivity is the extent to which actual positives are not overlooked (minimizing false negatives), and specificity is the extent to which actual negatives are classified as such (minimizing false positives). The *positive predictive value* (PPV) and *negative predictive value* (NPV) describe the performance of a diagnostic test. A high result can be interpreted as indicating the accuracy of such a test [29]. The false-positive rate is the proportion of all negatives that still yield positive test outcomes, i.e., the conditional probability of a positive test result given an event that was not present. *False-positive rate* is equal to the significance level. The specificity of the test is equal to 1 minus the false-positive rate. *False-negative rate* is the proportion of positives yielding negative test outcomes with the test, i.e., the conditional probability of a negative test result given that the condition being looked for is present.

Of note, false positives should be differentiated from the phenomenon of *overdiagnosis* [30]. The finding of an insignificant pulmonary nodule or an adrenal "incidentaloma" on a chest CT ordered for a patient with a suspected pulmonary embolism is an example of overdiagnosis. The use of CDS tools has the potential to minimize, or at least standardize, the use of advanced imaging technology in such cases.

By reviewing the 2 × 2 tables shown in Table 3.4, we can design the most efficient CDS questions or tests.

Key elements of CDS are best described in a quote from Wyatt and Spiegelhalter: "Active knowledge systems which use two or more items of patient data to generate case-specific advice" [31]. More specifically, leveraging a good foundational knowledge base along with patient-specific information such as vitals or laboratory results and using the most appropriate mode of communication will assist the user to make the most appropriate choice. As the user designs and builds their CDS, it is important to consider the following targets:

1. What are the desired outcomes/clinical targets of CDS?
2. How will the CDS tool improve efficiency?
3. Are we looking for early detection/screening of the CDS?
4. Can CDS assist in the diagnosis or treatment protocol?
5. Can CDS provide preventative adverse outcome?
6. Can CDS provide follow-up management?
7. How does CDS provide cost reductions/conveniences?

Other design considerations should include the target audience. Which member of the healthcare team is the target for CDS? Is the intervention targeted to patients or families? Also consider the level of control of the CDS (preemptive, suppressible, hard-stop, or interruptive). Preemptive or active CDS is a rule based upon simple logic or systems-based upon probability. Active CDS includes rules and alerts. Respectively, hard-stop or suppressible control levels either prevent the user from taking an action altogether or allow them to proceed only with the external override of a third party. Interruptive CDS occurs when a process is interrupted

Table 3.4 Table to derive sensitivity and specificity

Total Population	Condition Positive	Condition Negative	Prevalence
Predicted Condition Positive	***True positive***	***False positive***	Positive Predictive Value $\frac{True\ Positives}{True\ Positives+False\ Positives}$
Predicted Condition Negative	***False Negative***	***True Negative***	Negative Predictive Value $\frac{True\ Negatives}{False\ Negatives+True\ Negatives}$
	Sensitivity $\frac{True\ Positive}{True\ Positives+False\ Negatives}$	Specificity $\frac{True\ Negative}{True\ Negatives+False\ Positives}$	
	False Negative Rate $\frac{False\ Negatives}{True\ Positives+False\ Negatives}$	True Negative Rate $\frac{True\ Negatives}{False\ Positives+True\ Negatives}$	
True positive	Sick people correctly identified as sick		
False positive	Healthy people incorrectly identified as sick		
True negative	Healthy people correctly identified as healthy		
False negative	Sick people incorrectly identified as healthy		

Table 3.5 Example categories of clinical decision supports

Therapeutic duplication
Single and cumulative dose limits
Allergies and cross allergies
Contraindicated route of administration
Drug-drug and drug-food interactions
Duplicate orders
Contraindications/dose limits based on patient diagnosis, age, weight, prior laboratory, or radiology studies

and requires the user to acknowledge its information by taking one or more actions, such as in computerized order entry (CPOE) systems. Three types of interruptiveness are on-demand (link to formulary from within order), in-line or modeless (unread lab result notification on sidebar), and popup or modal (alerts or reminders requiring acknowledgment).

Table 3.5 shows some examples of CDS categories.

When designing CDS, the user should always ask themselves the following questions to make sure they have addressed the five "rights" to assess their success [32]:

1. Right information – quality of knowledge base
2. Right person – target of CDS
3. Right format – implementation of CDS (speed, ease of use, comprehensibility)
4. Right channel – mode of CDS
5. Right time – workflow integration

Do I have the right information for the question? Have I accessed the right knowledge base and provided the correct resources and references? Who is my target audience, and have I reached them successfully? Do I have my question in the right format? Am I providing them with knowledge only, or is my aim to stop the user's process or redirect them? Do I have my CDS in the correct spot to provide the user the correct additional knowledge to make an informed decision?

Having created a CDS plan or outline, the user will most likely need to submit a proposal to a CDS committee that oversees all CDS and provides continuous feedback for the system. Many institutions may have forms to complete or submit. You will see in Fig. 3.2 that the example CDS form request follows the "5 Rights."

David Bates summarized the goals and expectations for CDS in his 2003 AMIA article (Table 3.6) [33]. He believes it is key that information systems provide decision support to users at the time they make decisions, thus promoting improved quality of care. Providers make many errors, and clinical decision support should help identify and avoid such errors.

Clinical Decision Support Request Form

Person submitting the request	
Purpose of goal for the CDS	
Evidence-based need	**RIGHT** information *What are the clinical grounds and supporting evidence for the CDS?*
Intended audience	**RIGHT** person *Who will see it? - e.g., physicians, RNs, pharmacists, etc.*
Clinical champion(s)	*Who will be the clinical champion (s) responsible for the success of implementing this alert?*
Primary stakeholders	*Who are the primary group (s) or committee (s) that have a stake in this CDS? This is important, as they may need to sign off prior to enabling CDS.*
Established level of consensus?	*Do we know whether stakeholders all agree on need for CDS?*
Clinical criteria for the CDS	**RIGHT** time – workflow integration *When should the CDS be triggered?*
Impact on patienr care	*What is expected to change as a result of the CDS?*
Impact on workflows	**RIGHT** channel – mode of CDS *What groups, activities and workflows is the CDS limited to? What is the frequency that it will occur?*
Urgency	*What is the urgency for this CDS? Why is it urgent?*
Monitoring success of the CDS	**RIGHT** format – implementation of CDS (speed, ease of use, comprehensibility) *What specific outcomes will be used to determine success of the CDS?*
Future clinical review	*What is the expected frequency and method for future clinical review of the CDS?*

Fig. 3.2 Example of a clinical decision support (CDS) form request that follows the "5 Rights"

Table 3.6 Ten commandments for effective clinical decision support [33]

1.	Speed is everything – expect sub-second latency
2.	Anticipate needs and deliver in real time – e.g., showing relevant labs with med orders
3.	Fit into users' workflow – external tools are not as good as those at POC
4.	Little things can make a big difference – "usability matters – a lot," "make it easy to do the right thing"
5.	Physicians resist stopping – do not tell doctors to not do something without offering an alternative
6.	Changing direction is easier than stopping
7.	Simple interventions work best – try to fit guidelines onto a single screen
8.	Asked for additional information when you really need it – "likelihood of success is inversely proportional to the number of extra data elements needed"
9.	Monitor impact, get feedback, and respond. Evaluate your CDS
10.	Manage and maintain your knowledge-based systems. Keep up with clinical care

Information Technology Systems

Telehealth

The desire to constantly improve the access, delivery, and quality of healthcare has resulted in the application of novel technologies to nearly all domains of medicine. Telehealth, also referred to as telemedicine, is defined by CMS as the electronic transmission of patient information from one distant site to another and has evolved to also include electronic communication between patients and providers in order to facilitate healthcare. Telehealth can employ many different types of technology to achieve patient to clinician communication including telephonic, short message service (SMS), fax, email, and real-time audio-video communication utilizing Internet connectivity and computers.

The utility of telehealth is vast and constantly evolving. Commonly cited benefits include improved clinician access in rural areas where such expertise is not available, decreased healthcare costs, and increased healthcare system workforce resilience, as well as patient and provider convenience [34]. During the COVID-19 pandemic, telehealth was utilized as a mechanism to reduce the use of one-time use personal protective equipment [35]. Some patients report preferring telehealth in place of traditional in-person visits for certain encounters, such as for birth control prescriptions [36]. Immunocompromised patients, including oncologic and rheumatology patients, have utilized telehealth to limit pathogen exposure associated with in-person visits at healthcare facilities.

Case Study 1

A 65-year-old female with a history of acute promyelocytic leukemia (APL) presents by ambulance to a rural hospital emergency department (ED) with complaints of altered mental status and worsening rash. Her husband at bedside reports 1 day of fever, increasing confusion, and, most recently, epistaxis. On examination of her skin, a diffuse petechial rash is discovered.

The clinician at bedside recognizes the patient is likely in disseminated intravascular coagulation (DIC) likely due to her APL. Basic supportive interventions are initiated, and diagnostic testing is ordered to confirm the suspected diagnosis. The clinician recognizes that this patient would benefit from specialty consultation and transfer to a higher level of care. A tablet computer mounted on a bedside cart is then used to connect a live video communication with an oncologist hundreds of miles away. After consultation with the oncologist, a live encounter with the patient and spouse is performed by the remote physician. Written treatment recommendations are captured and electronically transmitted by the electronic health record (EHR) from the oncologist to the emergency physician, and transfer to a quaternary care center is initiated.

History of Telehealth Although telehealth is widely used today all across the globe, its origins began over 60 years ago with the application of live video to facilitate psychiatric evaluations [37]. The National Aeronautics and Space Administration (NASA) researched telehealth heavily throughout the 1960s–1970s, culminating in pilot studies delivering healthcare to astronauts during space travel [38]. The birth of the Internet in the early 1990s, coupled with increased use of consumer video conferencing applications such as Skype in the early 2000s, further advanced the adoption of real-time audio-video communications as a way to deliver healthcare.

Today, there are hundreds of software and hardware telehealth products and services. Many telehealth encounters are performed on smartphones or tablet computers, as such devices have become ubiquitous in many parts of the world. The integration of telehealth with remote biometric sensor technology has also created new opportunities, such as telehealth intensive care units (ICU) and remote stroke consultation. Although many clinicians today do not incorporate telehealth into their practice, some have elected to only practice by telehealth, often citing increased flexibility and consumer demand.

Technology The safe evaluation and care of patients in any environment or by any medium requires some basic standards in place, such as clear audio, adequate visuals, and

timely data access. These specific standards initially led to the development of specialized telehealth hardware such as high-definition cameras and microphones. Early hardware was often large, bulky, fragile, and expensive. Early telehealth efforts were hindered by lagging pixelated video and fragmented audio. As Internet bandwidth increased and wireless technology decreased barriers to bringing devices to patients' bedsides, older hardware was replaced with smaller, cheaper, and better-quality devices, often affixed to carts.

Along with advances in hardware came new specialized healthcare software: the electronic health record (EHR). The replacement of paper medical records by digital records further aided telehealth adoption, as patient records could be stored on servers or in the cloud to be accessed by clinicians quickly and remotely. Most modern EHRs also support computerized provider order entry (CPOE) allowing rapid electronic ordering and reporting of diagnostic tests and ordering of medication prescriptions. Some EHR vendors have now started building telehealth directly into their products.

Telehealth Regulation Telehealth in the United States, like much of healthcare generally, is highly regulated at both state and federal levels. Restrictions on telehealth traditionally fall under three main categories: allowable locations/applications, requirements of service, and billing. Rural patients without access to robust care were seen as the greatest beneficiaries of telehealth. This led to regulations limiting telehealth services in urban areas where the need was postulated to be less. Furthermore, limits on what types of encounters (ambulatory vs. inpatient) qualify for telehealth are commonplace. The requirements of service are also used to tier the classification for reimbursement of telehealth. For example, a simple telephone audio-only call may not qualify as telehealth despite robust history gathering. Regardless of what type of telehealth tier is being utilized, the patient must verbally consent to telemedicine services. The business viability of telehealth has heavily relied on reimbursement policy set by agencies such as the Centers for Medicare & Medicaid Services (CMS). Many telehealth services are not reimbursed at the same rates as corresponding in-person encounters.

Many federal and state telehealth regulations were revisited and changed to respond to the COVID-19 pandemic of 2020. This led to the single greatest expansion of telehealth services in history and ushered in a new era where telehealth is commonplace and widely accepted. One of the most notable changes regarded the enforcement of patient privacy and security requirements from the 2009 Health Insurance Portability and Accountability Act (HIPAA). Although HIPAA still applies broadly, the enforcement of high encryption standards in video conferencing software was deferred. This allowed free consumer-focused telecommunication applications such as Skype (Microsoft Inc., Redmond Washington), Zoom (Zoom, San Jose California), and Hangouts (Google, Mountain View California) to be used instead of expensive niche telemedicine platforms.

Oncologic Emergencies and Telehealth The use of telehealth in the prevention of oncologic emergencies is growing. Telehealth may be deployed to reduce exposure to infectious disease in cancer patients at higher risk (e.g., immunocompromised), and telehealth has the obvious potential to reduce ED visits among cancer patients. Telehealth can also facilitate continuity of clinician-patient care, bringing in valuable context from the patient's own specialist when traveling. Remote video consultation and evaluation by oncologic specialists in both regular and emergent capacities can also aid in the diagnosis and treatment of patients. Many rural locations lack robust medical care systems and specialist oncologic expertise can be scant. Much more research is needed on the impact of telehealth on patient outcomes.

Conclusion Telehealth provides powerful tools in the care of oncologic patients during emergencies. Rapid technological developments will continue to change how clinicians care for patients. Changes in the regulation of telehealth have greatly expanded its applications and viability as a regular component of healthcare in the twenty-first century. Leveraging telehealth to assist in the care of patients with oncologic emergencies will prove more common and more powerful in the years to come.

Security

As healthcare continues to innovate and advance, the use of technology to care for oncologic patients continues to evolve and grow. From Internet-connected medical devices to artificial intelligence and machine learning, healthcare is increasingly digitized, connected, and complex. In this era of hyper-connected healthcare, it is important to focus not only on the care of oncologic patients but also on cybersecurity and privacy of sensitive patient data.

Case Study 2

After a long and busy shift in the ED, an attending physician posts on social media the following statement: "Just had the honor to treat one of our nation's last surviving World War II veterans in the Emergency Department at General Hospital! Despite his chronic lymphocytic leukemia, Albert is going to be okay! #VeteransRock #CancerSucks." The next day, he is

Table 3.7 18 HIPPA patient identifiers

Name
Address (all geographic subdivision smaller than state, including street address, city-county, and zip code)
All elements (except years) of dates related to an individual (including birthdate, admission date, discharge date, date of death, and exact age if over 89)
Telephone numbers
Fax number
Email address
Social Security number
Medical record number
Health plan beneficiary number
Account number
Certificate or license number
Vehicle identifiers and serial numbers, including license plate numbers
Device identifiers and serial numbers
Web URL
Internet Protocol address
Finger or voiceprint
Photographic image – photographic images are not limited to images of the face
Any other characteristic that could uniquely identify the individual

called into an administrator's office and is subsequently terminated from his employment for violating the hospital privacy policy.

Health Insurance Portability and Accountability Act (HIPAA) The Health Insurance Portability and Accountability Act (HIPAA) was a law passed by the US Congress in 1996 that, among other things, provided regulation around the security of protected health information (PHI) [39]. Beyond defining PHI, this law provided 18 "identifiers" (Table 3.7) constituting sensitive data elements that can be used to identify and subsequently violate the privacy of patients. Additionally, the law established a reporting and enforcement mechanism to ensure parties responsible for protecting PHI could be heavily fined if they suffered a breach or were negligent in securing the data.

Today, HIPAA continues to be a very important part of healthcare regulation. It remains regularly enforced, leading many hospitals to devote significant resources to the protection of PHI and compliance with federal regulation. When PHI is lost or exposed, it is termed a breach. Breaches of greater than 500 patient records often result in mandatory reporting to the federal government as well as the patients whose records were compromised. Common causes of breaches include (1) failure to dispose of paper records properly, (2) loss of computers containing PHI, (3) hacking of records by malicious actors, and (4) loss or records by a third party that was trusted with records (e.g., healthcare contractor or business affiliate).

Conclusion In the care of oncologic patients, as with other patients, the security and privacy of their PHI is important. As healthcare continues to become more digitized, the risk of exposing this information increases. Federal law protects patient data privacy, and failure to protect these data can lead to significant harms to patients, providers, and organizations. Oncologic patients can be at particular risk of PHI breach as they are often high utilizers of healthcare resulting in more records and can carry sensitive diagnoses.

Communication

Order Sets

AMIA defines an *order set* as a predefined template. Order sets are lists of orders that frequently include medication, laboratory, nursing, diet, activity, and other orders. They existed prior to the advent of electronic health records as paper templates. A common example is an admission order set. This would frequently include an admission order, a diet order, nursing orders, vital signs, activity orders, IV orders, medication orders, laboratory orders, radiology orders, consultation orders, and provider preferences. Order sets allow physician to easily select from commonly used orders to save time and ensure consistency for certain procedures, such as a surgery, admission, or discharge [40].

AMIA indicates that order sets have been "…the standard of care in hospitals for many years. While in the past, it took the form of pen and paper, today, it is, indeed, electronic" [41]. The Institute for Safe Medication Practices (ISMP) has developed guidelines around order sets [42]. The ISMP indicates that well-designed order sets have the potential to "integrate and coordinate care by communicating best practices through multiple disciplines, levels of care, and services, modify practice through evidence-based care, reduce variation and unintentional oversight through standardized formatting and clear presentation of orders, enhance workflow with pertinent instructions that are easily understood, intuitively organized, and suitable for direct application to current information-management systems and drug-administration devices, decrease the potential for medication errors through integrated safety alerts and reminders, and reduce unnecessary calls to prescribers for clarifications and questions about orders" [42]. The ISMP goes on to state that order sets that "are not carefully designed, reviewed, and maintained to reflect best practices and ensure clear communication, they may actually contribute to errors" [42].

The astute observer will note that order sets have been used for many years to standardize workflows, remind providers, and make suggestions about clinical care that has been vetted by best practices and evidence. In the case of patients presenting to the ED, oncologic patients present a

unique challenge. These patients are frequently immunosuppressed, which leaves them susceptible to several unique conditions, such as those infections that only spread in the immunocompromised state (i.e., neutropenic fever) and that may present with various metabolic derangements, such as tumor lysis syndrome. Given the infrequency with which emergency physicians encounter these conditions and the morbidity and mortality associated with them, these cases are ripe for use of order sets. Oncologic emergencies also demonstrate the need for collaboration in design of order sets. Many large healthcare organizations have informatics teams of healthcare practitioners that work in concert with information systems (IS) personnel to develop content for their electronic health record (EHR). The oncologic emergency is an example where various stakeholders and specialties work together to develop content. Polling providers for preference, along with scouring the literature for recommendations and guidelines, is often the first step in designing an order set. Usually one or more clinical "champions" are identified to begin the process of consulting literature, guidelines, experts in the domain, and practitioners in the affected departments. Their next step is usually to form a working group of affected stakeholders. In this case, ED providers, oncologists, and nursing would likely comprise the group. The two specialties would then discuss recommendations for order sets and request feedback from their respective departments. Much like the legislative reconciliation process, the groups then rejoin, find common ground, and resolve differences. This design would then be submitted to IS for testing and, later, implementation. Once implemented, as indicated by the ISMP, a properly verified and scrutinized order set has the ability to standardize and improve care.

Transition of Care Tools

The order set itself is one way of communicating care standards. The literature on emergency physician to ambulatory provider and vice versa communication is sparse, but it demonstrates differences in communication preferences [43]. Transitions of care are a topic of much discussion and are heavily scrutinized by The Joint Commission [44]. This is especially the case after an ED visit. While not all visits to the ED or hospital are avoidable, there has been increased attention in recent years on avoiding as many visits as possible.

One factor contributing to avoidable ED visits is provider-to-provider communication. Open and clear communication decreases errors and costs [45]. Some health systems have found communication to be so important for patient care that caseloads have been limited to ensure that provider-to-provider communication takes place [46]. With all the focus on communication, one might assume this problem would have been resolved. However, communication is regularly cited for the last 15+ years as one of the major factors in malpractice cases, regulatory citations, and poor patient reviews [47].

Healthcare organization management has taken this seriously and imagined a variety of solutions. After the HITECH Act was signed into law, electronic health records (EHRs) adoption greatly increased. It was theorized that EHRs would foster provider-to-provider communication. Communication increased, but it was mostly asynchronous communication (i.e., email, text messages, assigning providers to notes, etc.). This was a different form of communication than existed previously, which was largely sharing information face-to-face or via telephone [48]. If these communications methods were equal in terms of patient care, this chapter would end early. Interviewees have indicated that EHRs allow for easier and more frequent asynchronous communication, though this does not remove the need for physician-to-physician communication. Learning from each other is much less likely to occur through an email as opposed to a phone call. Proposed solutions involving the EHR include building infrastructure to allow for "preferred mode of contact" and standardizing communications [48]. EHRs may assist with this, but if the workflow hasn't been designed prior to initiation, it's easy for staff to use more and more asynchronous communication.

In addition, proper configuration of EHRs is necessary to ensure that the right information flows to the right person, in the right format and channel, at the right time. These rights are collectively known as the "5 Rights of Clinical Decision Support" [49]. This is usually referenced regarding tools in the EHR, though the rights apply to any information in an EHR. Globally, it applies to communication in general. The authors recommend a similar approach to that applied for workflow analysis, order set design, and other aspects of informatics. This is to perform a thorough analysis of the situations in question, engage stakeholders and leaders, form consensus, test, implement, and review. The advantage of engaging leaders (or the early adopters) in the department or division is the outsized influence they may have on those resistant of adoption. It equally applies in the design of EHR implementation, design, and flow of information. It is *critical* to find the consensus on the preferred method of communication. When differences occur, technology may assist to resolve the issue of differing preferences.

At the authors' institution, the EHR was utilized to engage clinicians, administrators, researchers, and stakeholders by considering a patient visit for particular specified reasons as a "unit of communication." For a given patient visit, different stakeholders wished to be notified in different ways. Some clinicians preferred a text notification, while others preferred an email. Administrators preferred a spreadsheet or interactive database. Informatics personnel coordinated with lead-

ership in IS, the ED, ambulatory space, and leadership to develop a system that would create reports and send notifications to a group of providers. Review of the system after implementation demonstrated increased satisfaction for all parties involved. An additional bonus was closer to real-time data on those presenting to the ED for the identified reasons. Before this system, monthly SQL queries were necessary to create spreadsheets and graphs to monitor patient care. The new system utilized EHR tools and allowed those involved in care to easily identify the individuals affected, as well as relevant data to inform care processes.

The agreement on the pre-implementation of this plan led to less utilization of resources to better understand trends in the healthcare system. It also led to improved adherence with notification, as the prior system would not always notify the provider. Prior to implementation, ED staff was to send a secure email to the identified individuals. Adherence with this was poor, as the event was not common enough for the ED providers to implement the event in their workflow. For a variety of technical reasons, an order set for this scenario could not be implemented. However, enhanced communication was fostered utilizing the methods outlined in this chapter.

Research and Registries

Cancer Registries

A cancer registry is an information system that collects and analyzes data from a census of cancer cases. Registry data can be used to define and monitor cancer incidence, investigate treatment patterns, evaluate efforts to prevent cancer, and improve survival [50]. This allows public health officials and healthcare professionals to be apprised of cancer-related measures used to guide cancer prevention and control efforts.

Cancer data are collected in two different types of registries. Population-based registries are tied to state health departments, while hospital registries are a part of a healthcare organization's cancer program [51]. Population-based registries collect information on all cases within a certain geographic area from multiple reporting organizations including hospitals, doctors' offices, nursing homes, clinical labs, and ambulatory care organizations, as well as chemotherapy and radiation treatment centers. Hospital registries provide more complex data used to assess clinical care at a particular hospital. These data typically guide education of healthcare providers and focus on patient care. Pooled data can be used to observe trends with specific populations, providers, or locales [52, 53].

Cancer registrars with standardized training aid in collecting data for cancer registries. Registrars prepare accurate and timely data that is reported to the registry. Identifying individuals with cancer, or *casefinding*, is the first step in cancer registration. This is initiated during clinical care when physicians note the cancer site, type, stage, and patient demographics in the medical record. Registrars summarize and record other information for certain registries, such as treatments and follow-up to record recurrence and survival data [52]. The HITECH Act, through the electronic health record meaningful use program, incentivized case-based reporting.

Cancer Surveillance Programs

In 1971, the National Cancer Act was established which mandated collection, analysis, and sharing of cancer patient data in the United States for research, detection, and treatment of cancer. The National Cancer Institute established the first national cancer registry, the Surveillance, Epidemiology, and End Results (SEER) program, in 1973. This large population-based system of cancer registries provides data on cancer incidence, mortality, treatment, and survival [51, 53]. Data are collected regionally, representing 28% of the US population [51].

In 1992, the US Congress established the Cancer Registries Amendment Act which authorized the Centers for Disease Control and Prevention (CDC) to provide regional assistance to improve cancer registries, implement registries in absent regions, model legislation, provide training for registry personnel, set standards, and aid in establishing a reporting and data processing system. The National Program of Cancer Registries (NPCR) was established to accomplish these goals and supports cancer registries in 45 states, representing 96% of the population [53]. The NPCR and the SEER program, together, collect data for the entire United States.

Together with data regarding cancer incidence and death rates, cancer survival measures provide a comprehensive picture of the burden of cancer in a population and support public health efforts to prevent new cancers, extend survival and quality of life after a cancer diagnosis, and reduce cancer health disparities [50].

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Quality Measures

4

Tracy E. Spinks and Michael G. Purcell

Case Study: Addressing Unmet Palliative Care Needs in the ED

The medical director of an emergency department (ED) at a tertiary care center reviewed admission data for his cancer population. Over the past 12 months, he—along with colleagues—noticed a trend toward increasing admission rates in this population. On further evaluation of the primary admission diagnoses, the director found that many patients were being admitted for symptom control and palliative care consults. This equated to increasing admissions with prolonged hospital stays and contributed to consistently high hospital capacity. With the resultant decreased bed availability, the other admitted ED patients had longer wait times to arrive in an inpatient bed. The downstream effects directly contributed to ED boarding, longer ED wait times, and decreased patient satisfaction.

To address the issue, the director pulled together a focus group of providers to discuss the daily challenges surrounding cancer patients admitted for symptom control and palliative consults. It became apparent that often there is both discomfort and unfamiliarity of ED providers when it comes to dosing narcotics and antiemetics in this population as they are frequently on long-acting opioids and high doses of breakthrough medicines at home. The focus group expanded to include a member from the division of palliative care. A joint effort led to the creation of palliative care rounds, where the palliative care service would stop by the ED every morning to check in with care providers and assist with any question on symptom control for currently active patients. Additionally, the palliative care service worked to prioritize consults from the ED to help with early, aggressive symptom control and goals-of-care discussions. The primary goal was to improve symptom control and earlier palliative care access among cancer patients, as measured by two metrics: (1) hospital admissions among cancer patients for symptom control and palliative care consults and (2) palliative care consults in the ED.

After a 3-month pilot, the director reviewed the data. Admissions for symptom control and palliative care steadily declined over the 3 months, while palliative care consults in the ED steadily increased. Unintended benefits of the program led to improved emergency provider comfort with higher doses of narcotics and long-lasting opioids, improved relationships with the division of palliative care, and improved patient satisfaction with symptom control. The data were shared at the hospital's quality forum and hailed as a huge success.

Introduction/Background

Quality issues in oncologic emergency care are well-known. Common ED concerns include overcrowding, long wait times (perceived and actual), boarding, ambulance diversions, inadequate access to specialists, and patient handoffs. Additionally, some issues (e.g., receiving a late-stage cancer diagnosis in the ED) are not directly related to the quality of emergency care. Instead, they reflect broader cancer quality issues, such as inadequate access to and utilization of cancer prevention and diagnostic services, insufficient care coordination, fragmented healthcare delivery, poor symptom management, and underutilized hospice and palliative care services.

To address these and other healthcare quality issues, state and federal agencies have adopted quality measures assessing the underlying structures, processes, and outcomes of care for accountability, public reporting, and value-based payment programs. Despite the inherent appeal of public reporting and transparency of healthcare quality, there remains minimal evidence that public reporting of healthcare

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quality measures improves overall healthcare quality, reduces utilization, or influences healthcare consumer behavior [1–3]. In view of these observations—and to chart a path forward—it is important to consider the health policy and practice patterns that have contributed to historical issues with healthcare safety, appropriateness, effectiveness, and quality.

This chapter examines the history, current state, and desired future state of health policy for quality in oncologic emergency care. It explores known quality issues and upstream drivers and highlights the important role that quality measures can play in addressing these issues. Additionally, it outlines recommendations for measuring quality in oncologic emergency care and proposes healthcare policy changes and quality measures to drive these changes. Finally, it includes a sample case study describing how ED providers can partner with palliative care providers to reduce ED visits.

History and Current State of Health Policy for Quality in Oncologic Emergency Care

Emergency care lacks formal health policy to support the unique needs of patients with a cancer diagnosis. Existing health policy focuses on providers' duty to treat patients in an emergency along with patient access to emergency medical care. This section describes two key drivers of current health policy for emergency medicine—the no-duty-to-treat principle and the Emergency Medical Treatment and Active Labor Act (EMTALA). The sections that follow explore known issues in oncologic emergency care, contributing factors, and historical efforts to measure the quality of US emergency care.

The No-Duty-to-Treat Principle and the Emergency Medical Treatment and Active Labor Act (EMTALA)

The no-duty-to-treat principle—the controlling law in the USA for over a century—gives physicians significant autonomy in determining which patients they will serve [4]. Several state court cases have supported this principle and have generally held that duty-to-treat begins when the patient-provider relationship is established, regardless of whether the relationship is expressly agreed [5–10]. While the no-duty-to-treat principle remains the controlling law, federal and state entities have established safeguards—through statutes, regulations, and court cases—to prevent discrimination and to ensure access to emergency care [4, 11–18].

Enacted through the Consolidated Omnibus Budget Reconciliation Act of 1986 [19], EMTALA remains the most influential US law affecting emergency care. An "antidumping" law, EMTALA prohibits discriminatory practices in emergency care. The law obligates Medicare-participating hospitals with dedicated EDs to screen, stabilize, and, where necessary, accept transfer patients, regardless of insurance status, ability to pay, or existing relationship with the facility. EMTALA prohibits the transfer of medically unstable patients for any reason except medical necessity (e.g., for specialized emergency care that is unavailable at the transferring facility). EMTALA's screening, stabilization, transfer, and recipient provisions are considered absolute unless modified due to a disaster or public health emergency, such as the 2019 novel coronavirus outbreak [20, 21]. Violations carry heavy fines and can lead to suspension from the Medicare program.

Over time, EMTALA's provisions have been clarified through regulations, court cases, and statutes, including the Patient Protection and Affordable Care Act of 2010 (ACA). These actions clarified hospital responsibilities to staff on-call specialists and defined the physical locations that fall within EMTALA's jurisdiction. Importantly, protections under EMTALA do not apply to outpatients with scheduled nonemergency procedures, and hospitals' stabilization and transfer rights and duties terminate once a patient is admitted as an inpatient [4, 22–31]. Many EMTALA provisions remain controversial. For example, EMTALA facilitates critical access to emergency care but makes no provision for reimbursement of that care. Uncompensated emergency care exceeds uncompensated inpatient and outpatient care combined [32] and remains the burden of emergency care providers [33, 34]. Additionally, EMTALA does not address quality of care. Thus, as long as emergency care is delivered in good faith, misdiagnosis, delays, and medical negligence do not constitute EMTALA violations. EMTALA's stabilization obligations are considered absolute, even when such care is futile due to an underlying condition or when it conflicts with standard of care or a physician's moral and ethical judgment [4, 26, 30].

In summary, the no-duty-to-treat principle and EMTALA represent a strong policy framework to ensure patient access to emergency medical care in the USA. Nearly 35 years after its passage, EMTALA continues to provide essential protections to the nation's most vulnerable residents—the uninsured, underinsured, and disenfranchised—by prohibiting discriminatory emergency care. EMTALA's lasting consequence is the transformation of the US emergency care system into a de facto safety net to address access and financial barriers to primary care. A predictable, albeit unintended, outcome is that EDs are overloaded and inadequately funded to comply with this federal mandate [35]. This compromises

the quality and accessibility of emergency care for all patients, including those with a cancer diagnosis. Quality issues for oncologic emergency care are described in the next section of this chapter.

Known Quality Issues

In pursuing emergency care, patients with a cancer diagnosis encounter a mix of quality issues—both oncologic-specific and generalized. Moreover, many of these issues arise from inadequate access to care or quality issues in primary care and outpatient settings. Six issues that affect cancer patients in the emergency setting are described below: (1) late-stage cancers presenting to the ED; (2) overutilization of emergency services; (3) overcrowding, boarding, and diversion; (4) high costs at the end of life; (5) patient dissatisfaction with emergency care; and (6) caregiver burden. Specific issues for dedicated oncologic EDs are also discussed in this section.

Late-Stage Cancers Presenting to the ED

In a well-coordinated healthcare system, patients receive routine primary care and guideline-based cancer screenings, and cancer is diagnosed at an early stage in the primary care setting. However, many undiagnosed cancers present to the ED each year [36–40], with 11% of breast, prostate, colorectal, and lung cancers diagnosed in US EDs from 2004 to 2013 [41]. This is problematic for several reasons. First, these patients often present with generalized symptoms (e.g., nausea and vomiting, fatigue, and bleeding) that may indicate multiple underlying conditions. Moreover, emergency physicians may lack established relationships and a comprehensive medical background for these patients. Therefore, an accurate diagnosis and treatment may be further delayed until the patient seeks follow-up outpatient care or returns to the ED with continued symptom escalation. Second, cancers diagnosed in the ED tend to be of later stage and, therefore, poorer prognosis. Researchers have observed worsened outcomes, including lower overall survival, higher perioperative mortality and readmissions, and longer length of stay [37, 38]. Third, ED-diagnosed cancers suggest disparities in healthcare. For example, researchers at a Florida safety net hospital observed that African Americans, urban dwellers, and those without private insurance were more likely to have a cancer diagnosed in the ED and were at increased risk for stage IV cancer and death [38]. Similarly, a Michigan study of ED-based lung and colorectal cancer diagnoses noted that cancer diagnoses in the ED were disproportionate among older persons, African Americans, dual-eligible patients (patients eligible for Medicare and Medicaid benefits), and patients with three or more comorbidities. Of note, patients diagnosed with cancer in the ED had significantly more healthcare encounters (inpatient, outpatient, and primary care) in the months preceding their diagnosis [36]. This suggests a gap in the quality, rather than the quantity, of healthcare services. These findings highlight gaps in the nation's population health strategies and indicate opportunities for improvements in screening, early detection, care coordination, and patient education—particularly for more vulnerable populations.

Overutilization of ED Services

Cancer patients present to the ED with acute conditions, including sepsis, spinal cord compression, deep vein thrombosis, and respiratory and gastrointestinal obstruction. Emergency physicians, trained to diagnose and treat acute illness and injury and to stabilize patients for further treatment, are uniquely qualified to manage these emergencies. However, not all emergency visits by oncologic patients represent true oncologic emergencies. Duflos et al. and Wallace et al. observed potentially avoidable emergency visits at 48% and 52% of ED presentations, respectively [42, 43]. Also, Delgado-Guay et al. observed that patients receiving palliative care had a lower rate of avoidable ED visits (23%) [44]. Together, these findings suggest overutilization of emergency services for symptoms associated with progression of disease and treatment side effects that could be managed effectively in the outpatient setting, particularly with palliative care integration. Cancer patients often present with several interrelated symptoms, including pain, fatigue, dyspnea, nausea, dehydration, depression, and cognitive impairment. Chronic pain, in particular, is a frequent complaint among cancer patients visiting the ED. In the absence of highly coordinated multi-symptom management, cancer patients experience frequent ED visits, especially near the end of life [45]. Racial and socioeconomic disparities are a factor here as well [46]. Several observational studies have examined ED service utilization among cancer patients at the end of life. The findings of these studies vary—27–37% of the study populations had an ED visit in the last 14 days of life, and 7–19% of the study populations experienced multiple ED visits in the last 30 days of life [47]. In a 2010 study of hospice enrollees, Carlson et al. observed that patients who disenrolled from hospice were significantly more likely to have an ED visit compared to their continuously enrolled counterparts (33.9% vs. 3.1%) [48].

In the early 2000s, Earle et al. identified frequent ED visits as an indicator of poor quality of care [49, 50]. Aprile et al. concluded that over 50% of unplanned visits at an acute oncologic clinic were repeat presentations [51]. Repeat ED visits suggest healthcare quality issues across care settings.

For example, patients may receive inadequate symptom management, discharge instructions, or follow-up care as part of the initial ED visit. Alternatively, upstream access or care coordination issues may lead patients to seek emergency-based care that could be delivered in a less costly outpatient setting. In other cases, repeat ED visits indicate that patients—particularly those with complex comorbidities, diminished performance status, or poor prognosis—are receiving overly aggressive treatment (e.g., chemotherapy), where the treatment toxicities exceed the potential clinical benefits. Repeat ED visits may also indicate delayed access to hospice and palliative care services or that caregivers are not prepared to manage and cope with the burden of cancer disease at home. These trends highlight the need for more selective use of aggressive treatment, improved symptom management, and earlier introduction of advance care planning. Likewise, greater access to palliative and hospice care, same-day/next-day physician appointments, and 24/7 access to providers may reduce ED utilization by cancer patients, particularly at the end of life. These care delivery approaches are discussed later in this chapter.

Overcrowding, Boarding, and Ambulance Diversion

The demand for emergency services routinely exceeds ED capacity, particularly in large urban areas. Due to coalescing system-level issues, including ED closures, inadequate or delayed access to primary and specialty care, and higher rates of uninsurance and underinsurance, ED overcrowding has worsened over time [52]. ED crowding is worsened by ED "boarding," where admitted patients remain in the ED for hours—*even days*—until a hospital bed becomes available. Sadly, ED boarding has become a routine practice for most EDs and reflects high inpatient census rates and inefficient admission processes [35]. More than an inconvenience, ED overcrowding and extended ED boarding have been associated with poorer quality of care and patient experience and may disproportionately affect older, sicker patients and those requiring specialized inpatient care [53]. Key indicators include treatment delays, patients leaving the ED without being seen, increased risk for medical errors (including medication errors), and multiple poorer outcomes, including longer lengths of stay and higher inpatient mortality rates [53–57].

Unmanaged ED crowding and prolonged ED boarding contribute to ambulance diversion. Once a practice reserved for catastrophic events, diversion has become increasingly common, especially in urban areas. By delaying treatment or by redirecting patients to EDs without the resources and expertise to optimally care for their severity of illness, diversion can place patients with acute conditions at significant risk [35]. Furthermore, extended diversion time has been associated with adverse patient outcomes, particularly for patients with life-threatening conditions [58, 59]. Together, ED overcrowding, extended boarding, and ambulance diversion increase stress among ED providers along with patients' risk for adverse events and poorer outcomes. Accordingly, experts have advocated for stronger standards to reduce these practices [35]. While these findings and recommendations are not specific to oncologic emergency care, they have important implications for cancer patients seeking ED care.

High Costs at the End of Life

In 2010, an estimated $38 billion was spent on end-of-life care for cancer patients in the USA. By 2020, those costs were projected to increase to between $49 billion and $74 billion, representing up to 36% of total spending for cancer care [60]. Underlying factors include healthcare fragmentation, frequent transitions between care settings, inadequate care coordination, no or delayed access to palliative and hospice care, and overutilization of aggressive treatment for patients with advanced disease. Additionally, despite efforts to transition to value-based care, most cancer care is still reimbursed as fee-for-service, which creates financial incentives for providers to deliver high-cost and high-intensity services, even at the end of life. Vera-Llonch et al. estimated total healthcare spending at nearly $126,000 and $129,000 for patients receiving chemotherapy for metastatic lung cancer and metastatic breast cancer, respectively [61, 62]. A study of patients with stage IV breast, colon, lung, and prostate cancers observed that one-third of patients received a high-cost advanced imaging study (computerized topography or CT, magnetic resonance imaging or MRI, positron emission tomography or PET, and nuclear medicine or NM) in the last month of life, with the top 10% receiving three of these imaging studies [63]. A multinational study on site of death found that the USA had the lowest proportion of inpatient deaths among cancer patients (22%) but double the ICU admissions and length of stay in the last 30 and 180 days of life [64]. These findings suggest a higher intensity of care at the end of life in the USA when compared with other developed nations [65]. A recent study of patients with metastatic non-small cell lung cancer in the National Cancer Database indicated that 10.8% and 24.5% of patients initiated first-line treatment within 4 and 8 weeks of death, respectively [66]. Aggressive treatment at the end of life contributes to unsustainable national healthcare spending on end-of-life care without comparable benefit in terms of better survival, quality of life, and access to care. Since Americans have ranked treatment costs and financial burden to family members as their biggest concerns when faced with a life-limiting illness [67, 68], excessive health-

care costs exacerbate emotional distress among patients with a poor prognosis.

Significant geographic and between-hospital variation in end-of-life costs has been observed. A seminal study by the Dartmouth Atlas Project identified the availability of healthcare resources, rather than patient acuity or patient preference, as the most significant contributing factor [69]. A committee convened by the National Academy of Medicine, or NAM (neé Institute of Medicine), attributed 89% of variation in total Medicare spending to variation in acute care and post-acute care [70]. These findings have important implications to begin addressing overutilization of services (including ED visits) at the end of life and suggest that better care coordination may reduce spending for these patients.

Patient Dissatisfaction with Emergency Care

ED overcrowding, poor patient handoffs, and extended wait times—perceived and actual—compromise patient experience and contribute to patients leaving the ED without being seen [45, 71, 72]. Patient experience with ED care has not been systematically measured in the USA. However, researchers within and outside the USA have identified promoters and detractors of patient satisfaction with emergency care, with mixed results [73–75]. Overall satisfaction has been associated with provider interpersonal skills—communication, courtesy, empathy, and competence—and patient perception regarding wait times [75–78]. ED physicians often lack an established relationship with patients and carry heavy patient loads of varying acuity, leading to significant challenges to timely and accurate communication [79]. Patient satisfaction may be improved by training ED providers to initiate more frequent and targeted communication, particularly regarding wait times, and by expanding ED provider access to patient records across care delivery systems.

Some studies have demonstrated higher satisfaction among ED patients of higher acuity (and vice versa) [80–82]. Additionally, lower-acuity patients have expressed greater dissatisfaction with wait times and costs of care than their higher-acuity counterparts [82]. This difference may be attributed to two factors. First, urgent or emergent ED patients likely will be triaged more quickly than their nonurgent counterparts. Second, the fact that lower-acuity patients could be seen more quickly—and at a lower cost—in an outpatient setting may contribute to their dissatisfaction. Redirecting lower-acuity patients from the ED to more appropriate outpatient settings may help address this issue along with easing ED overcrowding and reducing total costs of care.

In 2012, the Centers for Medicare & Medicaid Services (CMS) funded initial work on a Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey for emergency care—the ED CAHPS (formerly Emergency Department Patient Experience of Care, or EDPEC, Survey). Development, testing, and refinement of the survey were completed in 2020. The 35-item survey, which assesses frequency of positive experience with ED processes, staff, healthcare received, and overall experience, received the CAHPS® trademark in March 2020. The ED CAHPS, Version 1.0, includes four composite measures (getting timely care, how well doctors and nurses communicate, communication about medications, and communication about follow-up) and two global measures (overall ED rating and willingness to recommend the ED) for patients discharged to home [83]. Currently, ED CAHPS use is voluntary, and providers are not required to report their results publicly. Nevertheless, early adoption of this survey will yield important insights regarding opportunities to improve patient experience with ED care.

Caregiver Burden

When caring for relatives with debilitating and chronic conditions, such as cancer, family caregivers experience significant financial, social, physical, and psychological distress. As cancer care continues to shift to outpatient settings, caregivers face increasing pressure to help their loved one navigate a complex and fragmented care delivery system and to care for their loved one at home while receiving limited training and support [84]. A 2011 survey from AARP, Inc. and the United Hospital Fund noted that 46% of caregivers of patients with multiple chronic conditions reported performing medical care (e.g., medication management and operating specialized medical equipment) for their loved one. Additionally, 53% of caregivers reported serving as care coordinators [85].

Several studies have described morbidity in caregivers of cancer patients [86]. Braun et al. reported that nearly 39% of caregivers of patients with advanced cancer experienced significant symptoms of depression [87]. Grunfeld et al. observed that caregivers of patients with advanced breast cancer experienced anxiety and depression that matched or exceeded the patient's anxiety and depression [88]. Wright et al. noted that place of death affected caregiver well-being. Death in the ICU or inpatient setting increased caregiver risk for post-traumatic stress and prolonged grief when compared with death at home [89]. Researchers have also described lifestyle interference among caregivers of cancer patients. Wadhwa et al. determined that 25% of caregivers of persons with advanced cancer experienced a change in work status [90], while Mazanec et al. estimated a 23% loss of work productivity among caregivers [91]. This is problematic, since increased lifestyle interference increases caregiver emotional distress [92] and can compromise their ability to provide

logistical and emotional support to the cancer patient [93]. Caregiver emotional distress can also negatively affect patient well-being. Two longitudinal studies of partners of breast cancer patients revealed that patient fatigue, symptom distress, anxiety, and depression increased in parallel with caregiver emotional distress [94, 95].

To prepare family members for caregiver role demands, the NAM recommended that healthcare agencies, including the Department of Health and Human Services (HHS), fund demonstration projects to train caregivers of cancer patients for their demanding role [84]. Federal and state lawmakers have also prioritized caregiver support through recent legislation—the Recognize, Assist, Include, Support, and Engage (RAISE) Family Caregiver Act of 2017 [96] and Caregiver Advise, Record, Enable (CARE) Act, signed into law in 39 states [97]. Yet, additional research and real-world implementation guidance are needed for meaningful change. Experts have identified interventions focused on caregiver skills and decision support, stress reduction, interdisciplinary palliative care, and psychosocial support to reduce caregiver burden, but such interventions remain largely untested [98, 99]. Caregiver training should focus on evolving caregiver needs throughout the continuum of care since short-term caregiver training has shown promising results [100], but caregiver-perceived preparedness, quality of life, and psychological well-being may diminish over time [101]. Professional and patient advocacy organizations can play an important role in developing educational materials and supporting programs to help caregivers manage their distress and provide optimal support for cancer patients [98].

Specific Issues for Dedicated Oncologic EDs

Dedicated oncologic EDs face additional pressures related to access and care coordination. Some patients with a cancer diagnosis seek entry to a comprehensive cancer center through the center's dedicated ED, if one exists [102, 103]. Additionally, EDs at other hospitals may seek to transfer uninsured or underinsured cancer patients to a specialized cancer center through its dedicated ED on the basis of an oncologic emergency that the transferring center is unable to manage. In these cases, the ED may serve as an interface or gateway into specialized oncologic care systems. However, there is no guaranteed access to oncologic care. Under EMTALA, the dedicated oncologic ED has the duty to screen and stabilize the patient in the ED. However, there is no duty to admit the patient, once stabilized, for further treatment of the patient's cancer diagnosis or other health issues. Even if active cancer treatment (e.g., chemotherapy) is required to stabilize the patient, there is no requirement to continue the treatment beyond the initial emergency presentation [104]. Thus, cancer patients may be bounced between multiple care settings, placing them at greater risk for receiving unsafe and poorly coordinated care.

Upstream Drivers

In the preceding section of this chapter, we discussed six quality issues affecting oncologic emergency care and described specific issues for dedicated oncologic EDs. Often, these issues arise when cancer patients seek ED care, but they are more directly associated with inadequate access to care or primary care gaps. Six upstream drivers that compromise ED-based oncologic care are described below: (1) poor care coordination; (2) underutilized advance care planning; (3) inadequate access to palliative care; (4) delayed hospice referral and the hospice reimbursement model; (5) limited availability of immediate and after-hours outpatient care; and (6) unrealistic patient/caregiver expectations regarding prognosis and treatment.

Poor Care Coordination

Fragmented healthcare delivery and inadequate care coordination are common among the elderly, the uninsured and underinsured, and patients with chronic and life-threatening conditions. Cancer patients may experience fragmented care across the cancer care continuum [105–109] as they frequently move between oncologic care, primary care, community and specialty hospitals, EDs, hospice, and long-term care. Indeed, the NAM identified nearly 30 clinical roles and disciplines involved in cancer care [84]. Specific issues relate to follow up on abnormal findings, management of comorbid conditions and symptom burden, medication administration (including chemotherapy), psychosocial support, end-of-life care, and survivorship transitions [105–116]. Increasingly, hospital outpatient departments are the care setting for complex cancer treatment [117], including stem cell transplantation, cancer surgery, and immunotherapy. Shifting these services from inpatient to outpatient settings has many benefits for patients, reduces healthcare costs, and eases the demand for inpatient resources. However, it places patients at increased risk for unmanaged pain, infection, febrile neutropenia, anemia, dehydration, nausea and vomiting, gastrointestinal distress, and dyspnea that lead patients to seek care in the ED. Thus, ED visits and, in particular, repeat ED visits may indicate unmet patient needs in other settings or that caregivers are unprepared to care for their loved one's disease at home. This is especially true at the end of life, when cancer patients present at the ED with poorly managed symptoms or progression of disease.

In the face of inadequate care coordination by the primary oncologic team, ED providers may become de facto onco-

logic care coordinators. However, ED physicians are trained to manage acute injury and illness and to stabilize patients for further treatment. Moreover, emergency physicians may be uncomfortable with addressing end-of-life issues in cancer patients [71]. Therefore, overextended physicians feel increasing pressure to ensure that patients are directed to appropriate follow-up care (including hospice or palliative care) and to close the loop with primary care physicians and oncologic providers. Strong care coordination, starting with a well-defined interface between primary care providers and oncologists [108, 109], is imperative to address fragmented cancer care. Both formal and informal primary care/oncologic relationships can improve care coordination [118], leading to improved handoffs and more appropriate healthcare utilization [119] and lessening the burden on ED care teams.

Underutilized Advance Care Planning

Advance care planning enables patients to consider their end-of-life preferences; to communicate those preferences to their family members, caregivers, and healthcare providers; and to document their preferences regarding life-sustaining procedures in a legally binding advance directive. Ideally, advance care planning begins during treatment planning, is documented by providers using structured templates [120], is informed by educational aids [121], and is revisited throughout treatment at clinically relevant time points (e.g., if the patient's prognosis worsens). In the context of cancer treatment, it should include ongoing communication between patients, caregivers, and providers across care delivery settings. The National Comprehensive Cancer Network (NCCN) recommends early initiation of advance care planning using a tailored approach based on where the patient is in his/her cancer trajectory [122]. For patients with advanced disease, advance care planning is critical to delivering patient-centered care and is essential to align treatment plans with patient values and preferences for quality of life, treatment intensity, and life-prolonging treatment. Early findings indicate that advance care planning has several benefits: reduced aggressive treatment and increased hospice referral at the end of life [123]; fewer ICU admissions; hospitalizations and inpatient deaths in the last 30 days of life [124]; clearer and earlier understanding of patient prognosis [125]; better alignment between patient preferences and care at the end of life [126]; and improved satisfaction and reduced stress and anxiety for patients and their families [127]. Despite fears to the contrary, it is not associated with increased hopelessness and anxiety for patients with advanced disease [128, 129].

Despite the potential benefits of advance care planning, end-of-life care discussions are often delayed until all curative treatment options are exhausted [130] and death is imminent [131]. Furthermore, researchers have observed large proportions of cancer patients presenting to the ED without an advance directive [132, 133]. Even when an advance directive exists, ED providers may be unable to access it in time to honor the patient's wishes regarding life-prolonging treatment when the patient presents with a sudden acute, life-threatening complication or critical decline in health status.

Of note, efforts to improve advance care planning have focused on executing advance directives for patients with poor prognosis. Advance directives are integral to advance care planning. However, advance care planning is much broader [122, 134] and includes thoughtful consideration of patient preferences regarding life-sustaining procedures, treatment intensity, quality of life at the end of life, and place of death. Goswami et al. and Pajka et al. have shown promising results in engaging advance practice nurses and ED staff in advance care planning [135, 136]. Future efforts should focus on coordinated, systematic, and patient-centered approaches to initiate advance care planning much earlier in the trajectory of disease, especially for patients with later-stage diagnoses.

Inadequate Access to Palliative Care

Palliative care addresses the physical and psychosocial effects of the disease and its treatment, thereby easing the burden of cancer throughout the continuum of care. Researchers have proposed early introduction of palliative care as an important strategy to improve symptom management and quality of life [137, 138], to help patients have more realistic expectations regarding their cancer [139], to reduce healthcare spending and utilization of acute care and emergency services [140, 141], and to improve survival in some patients [142]. Conversely, poor health-related quality of life has been associated with worse survival [143–146]. In the twenty-first century, the USA has seen substantial growth in palliative care programs [147–150]. Between 2009 and 2018, outpatient palliative care programs increased among NCI-designated cancer centers (59–95%) and non NCI-designated cancer centers (22–40%) [149]. Similarly, in 2019, inpatient palliative care programs were identified at 72% of hospitals with 50 or more beds (vs 67% in 2015 and 7% in 2001). This growth was concentrated among hospitals that are large (300 or more beds), urban, public or nonprofit, and located in northeastern states [150]. Thus, despite this increased capacity, palliative care services are not readily accessible for many cancer patients or may not be offered on a timely basis. Experts have suggested that palliative care referrals may be delayed due to erroneous perceptions among oncologists that palliative care and curative treatment must follow sequential pathways. Consequently, palliative care needs remain unmet, and patients with distress associated

with advanced disease or high symptom burden frequently seek care in the ED, particularly at the end of life.

To reduce barriers to timely palliative care, researchers have recommended colocation of outpatient oncologic and palliative care [151, 152] along with integrating palliative care with ED services [153–155]. Early studies suggest the benefits of ED-based palliative care programs, including better quality of life, reduced length of stay, lower intensive care, and improved hospice utilization, though the data are conflicting [156–159]. Researchers have identified several barriers to ED-integrated palliative care; these include inadequate palliative care training, an ED culture that favors aggressive treatment, and provider fear of being sued [160–163]. A multi-stakeholder workgroup convened in 2009 by the Agency for Healthcare Research and Quality (AHRQ) and the American College of Emergency Physicians (ACEP) identified four research priorities to address these barriers:

1. Which patients are in greatest need of palliative care services in the ED?
2. What is the optimal role of emergency clinicians in caring for patients along a chronic trajectory of illness?
3. How does the integration and initiation of palliative care training and services in the ED setting affect healthcare utilization?
4. What are the educational priorities for emergency clinical providers in the domain of palliative care? [164]

Interest in these areas has surged in recent years, particularly in testing different models of ED-based palliative care and the impact on healthcare utilization. Perhaps the greatest progress has been in the development and dissemination of guidelines, toolkits, and educational materials to advance palliative care in the ED [163, 165–171]. Continued experimentation and socialization are needed to drive clinical transformation in this important field.

Delayed Hospice Referral and the Hospice Reimbursement Model

Hospice programs that offer team-based comprehensive and interdisciplinary care can improve comfort and quality of life for cancer patients with a life expectancy of 6 months or less. Moreover, hospice referral is associated with higher quality care, including fewer hospitalizations, ICU admissions, and inpatient deaths and lower costs of care [172, 173]. Electing hospice care requires Medicare beneficiaries to forgo curative treatment and is appropriate when the risks or complications of treatment outweigh the potential benefits. Hospice referrals have increased significantly since the Medicare hospice benefit was created by the Tax Equity and Fiscal Responsibility Act of 1982 [174]. Over 1.5 million Medicare beneficiaries, representing over 50% of Medicare decedents, received hospice services in 2018. Cancer patients continued to lag behind their non-cancer counterparts in terms of hospice utilization. The share of hospice decedents with cancer declined from 52% to 26% between 2000 and 2018. In 2018, average and median length of hospice stay for cancer decedents were 53 and 17 days, respectively, versus average and median length of stay for decedents with neurological conditions (151 and 38 days, respectively). Together, these factors indicate that many cancer patients are enrolling in hospice too late to benefit fully from the team-based comprehensive and interdisciplinary palliative care that hospice programs offer [175].

Several barriers have been identified to earlier hospice referral. These include financial incentives to keep patients in the acute care system, provider discomfort with initiating end-of-life discussions, and patient and family difficulty accepting a terminal cancer prognosis [175]. Desired intensity of care remains a significant barrier to earlier hospice enrollment in the USA where patients with a terminal disease (defined as a life expectancy of 6 months or less) must agree to forgo curative treatment to qualify for the Medicare hospice benefit. Once patients are enrolled, Medicare pays hospice providers a per diem rate per enrollee. Under this capitated model, reformed in 2016 to better align reimbursement with the intensity of care delivered [176], hospice providers assume financial responsibility for all care related to the patient's terminal illness. Patients with advanced cancer often benefit from palliative radiation and chemotherapy, opioids, and parenteral nutrition. The treatment costs may be substantial and greatly exceed the Medicare hospice benefit. Accordingly, hospice providers may be discouraged from enrolling high-cost cancer patients, or they may implement restrictive enrollment policies aimed at cost control. These restrictions present many patients and caregivers with the dilemma of electing hospice care or comfort care at the end of life [177].

Concurrent cancer treatment and hospice care has been proposed as an effective remedy to address the limitations of hospice benefit design. In the early 2000s, the Robert Wood Johnson Foundation funded 22 demonstration projects of concurrent curative treatment and palliative care. These projects demonstrated early feasibility of an integrative approach to cancer treatment and hospice care across various patient populations and care settings [178]. Aetna conducted a similar pilot—extending hospice eligibility to patients with a life expectancy of 12 months or less—and observed increased hospice enrollment, lower utilization of acute care services, and a 22% reduction in costs [179]. Through its Comprehensive End-of-Life Care Initiative, started in 2009, the Veterans Health Administration offers concurrent cancer treatment (chemotherapy or radiation) and hospice services with good results. Studies conducted in patients with meta-

static non-small cell lung cancer demonstrated increased hospice utilization, less aggressive treatment at the end of life, and lower costs of care [180–182]. Success was associated with preserved hope and better quality of life among patients along with smoother transitions, stronger care coordination, and more frequent touch points with care teams. Concern regarding compliance with Medicare's either-or policy (i.e., cancer treatment or hospice) was cited as a potential barrier [183]. In 2016, the Center for Medicare and Medicaid Innovation (CMMI) launched the 4-year Medicare Care Choices Model to test concurrent cancer treatment and hospice in the Medicare and dual-eligible population (as authorized under the ACA) [184]. Experts have identified design limitations, including restrictive eligibility criteria. Early findings have revealed both challenges and successes. Hospice attrition initially was high, and beneficiary enrollment is much lower than expected. Advance care planning has been widely utilized. Both patients and caregivers have reported positive experience with care. Perhaps the pilot's greatest success has been improved utilization of hospice services (including counseling and symptom management) among enrolled cancer decedents. This suggests that concurrent cancer treatment and hospice may serve as a bridge to traditional hospice enrollment by offering patients and caregivers more time to process the patient's prognosis and treatment options while receiving supportive care [185, 186]. Additional demonstration projects are needed across federal, state, and commercial insurers to ensure that hospice benefit design promotes better quality of life, timely hospice enrollment, and, where appropriate, concurrent cancer treatment and hospice.

Limited Availability of Immediate and After-Hours Outpatient Care

Experts suggest that many ED visits are for non-emergent complaints that are more appropriately managed in the outpatient setting. Hansagi et al. observed that two-thirds of ED patients in their study were primary care cases, but the patients could not get in to see their physician or were referred to the ED for care [81]. Similarly, in an observational study of ED visits in North Carolina, Mayer et al. found that 44.9% of ED visits occurred during normal clinic hours and fewer than one-fifth of those patients were admitted to the hospital [187]. These findings underscore the need for more immediate access to outpatient oncologic care, such as through same-day/next-day appointments or 24/7 provider access.

The effectiveness of these practices is being tested through oncologic-specific patient-centered medical homes (PCMH). A primary care delivery model, the PCMH is designed to provide comprehensive, well-coordinated, patient-centered care by promoting access to preventive, chronic, and acute care, as well as a systems-based approach to safety and quality [188]. The Patient-Centered Outcomes Research Institute funded a 5-year PCMH model pilot with five medical oncologic practices in Pennsylvania. The pilot demonstrated greater access to specialty care and improved patient experience with shared decision-making but no change in ED visits and inpatient admissions [189, 190]. A broader pilot—Community Oncologic Medical HOME (COME HOME)—funded by CMMI [191] piloted similar approaches, including active disease management, triage and clinical pathways, enhanced provider access, and interdisciplinary teams, to deliver more coordinated cancer care. This pilot, implemented in seven community oncologic practices, produced a 10.2% reduction in ED visits and lower costs of care [192, 193]. These models of care should be studied further to determine the generalizability of these approaches to cancer care in the community and at academic medical centers.

Unrealistic Patient/Caregiver Expectations Regarding Prognosis and Treatment

Patient preference for intensity of treatment is influenced by health literacy, provider mistrust, family dynamics, religious beliefs, and other cultural and religious factors [194]. Cancer patients must have an accurate understanding of their treatment options and prognosis to avoid unnecessary, futile care and make treatment decisions that are consistent with their preferences and values. Indeed, patients that overestimate their prognosis are more likely to receive aggressive treatment of questionable benefit [195], while patients who understand their prognosis prefer symptom-directed care [131]. Several studies have confirmed that patients with advanced disease frequently misunderstand the intent of their cancer treatment and overestimate their prognosis [137, 196–198]. For example, Temel et al. published a study of newly diagnosed patients with metastatic lung cancer in 2011, noting that 32% of respondents considered their cancer curable and that 69% of respondents believed they were receiving curative, rather than palliative, treatment [139]. Likewise, Weeks et al. reported that 69% and 81% of patients with metastatic lung and colorectal cancer, respectively, did not understand that they were receiving palliative chemotherapy [195].

Communication challenges between patients, their caregivers, and providers contribute to patient and caregiver misunderstandings about prognosis or treatment intent. In some cases, patients receive accurate prognostic information, but do not understand or do not accept their prognosis. In other cases, physicians may be reluctant to provide this information, will do so only when asked by the patient, or will provide inflated survival estimates to their patients [195, 198,

199]. Mack and Smith attributed provider communication issues to discomfort with these discussions, uncertainty in estimating prognosis, and concerns regarding reduced hope, patient depression, and cultural appropriateness [200]. In 2013, the NAM recommended five strategies for improving patient-centered communication and shared decision-making for cancer patients:

1. Making more comprehensive and understandable information available to patients and their families
2. Developing decision aids to facilitate patient-centered communication and shared decision-making
3. Prioritizing clinician training in communication
4. Preparing cancer care plans
5. Using new models of payment to incentivize patient-centered communication and shared decision-making [84]

Implementing these approaches will assist providers in communicating more clearly regarding treatment intent and prognosis and will contribute to more realistic assessments among patients and their caregivers. Moreover, physicians should seek to understand their patients' preferences for prognostic information and adapt their communication styles accordingly.

Role of Quality Measures

Healthcare quality measures offer quantitative and qualitative assessments of the healthcare delivery. Experts have developed healthcare quality measures to evaluate the underlying structures and processes, outcomes, patient experience, and, to a limited degree, the costs of care. Moreover, there is increasing interest in measuring caregiver burden and experience with care. Some measures are developed for specific health conditions (e.g., breast cancer) or care delivery settings (e.g., ED), while other measures are crosscutting and apply to multiple health conditions or care delivery settings.

In this section, we describe the history of quality measurement in emergency medicine, provide examples of existing ED quality measures that are relevant to cancer care, and discuss the limitations of these measures.

History of Quality Measurement in Emergency Medicine

National quality measurement for emergency medicine began in the early 2000s as part of CMS' Reporting Hospital Quality Data for Annual Payment Update (RHQDAPU) program. The RHQDAPU program was a voluntary CMS quality reporting program that became the Inpatient Quality Reporting (IQR) program in 2010. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) introduced financial incentives for hospitals to report data on ten quality measures for pneumonia, acute myocardial infarction (AMI), and congestive heart failure via the RHQDAPU program [201, 202]. These measures were developed through the Hospital Quality Alliance, a public/private partnership with membership from CMS, the The Joint Commission, the American Hospital Association, and healthcare consumer groups [203]. In 2004, these data were published as the first national comparative dataset for ED quality. The financial incentives created under the MMA were later strengthened by the Deficit Reduction Act of 2005 (DRA) [204] and expanded to include measures for hospital-based outpatient care under the Tax Relief and Health Care Act of 2006 [205]. In 2015, Congress consolidated physician-focused federal quality programs through the Merit-based Incentive Payment System (MIPS), a key component of the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) [206].

Over time, ED quality measurement has been expanded through public and private sector efforts. In 2006, the American Medical Association's Physician Consortium for Performance Improvement (AMA-PCPI), ACEP, and NCQA co-developed physician-level ED measures for pneumonia, chest pain, and syncope [207, 208]. Additional independent measure development projects were undertaken by hospitals, by CMS, and by professional organizations, such as ACEP. These efforts focused on specific aspects of care (e.g., timeliness of care and ED communication). Disease-specific measures of morbidity, mortality, and resource use were also developed [208, 209]. At two Performance Measures and Benchmarking Summits convened in 2006 and 2010, participants proposed a wide range of metrics: operational metrics (e.g., ED census), timestamp and interval metrics (e.g., ED length of stay), proportional metrics (e.g., left without being seen), and utilization metrics (e.g., specialty consultations) [210, 211]. Stone-Griffith et al. developed the ED Dashboard and Reporting Application to support data-driven ED performance improvement projects by routinely measuring ED throughput [212].

In parallel, the National Quality Forum (NQF), a nonprofit organization that uses a consensus development process to endorse healthcare quality measures for use in federal public reporting programs, launched a two-phase project endorsing a national measure set for ED care. Between 2007 and 2009, the NQF endorsed 22 measures for ED care, including nine measures that were given time-limited (or temporary) endorsement and pending completion of measure testing and validation [213]. Subsequent projects focused on regionalized emergency care, care transitions, and chief complaint-based performance assessments [214–217]. These measures are included in Table 4.1. Some of these measures have been adopted for CMS public reporting programs,

Table 4.1 National Quality Forum-endorsed measures for emergency care: past and present

NQF ID	Measure title*	Measure description*	Reporting level	Measure owner*,†	Measure target (type)*	Year endorsed	Current status	CMS program‡	Relevant to cancer care?§
0004	Initiation and Engagement of Alcohol and Other Drug Abuse or Dependence Treatment	The percentage of adolescent and adult members with a new episode of AOD abuse or dependence who initiate treatment through an inpatient AOD admission, outpatient visit, intensive outpatient encounter, partial hospitalization, telehealth, or medication-assisted treatment (MAT) within 14 days of the diagnosis; the percentage of adolescent and adult members with a new episode of AOD abuse or dependence who initiated treatment and who had two or more additional AOD services or MAT within 34 days of the initiation visit	Health plan	NCQA	Behavioral health (process)	2009	Endorsed	PQRS, QRUR, VBM, QHP QRS	Yes
0025	Management Plan for People with Asthma	Percentage of patients for whom there is documentation that a written asthma management plan was provided either to the patient or the patient's caregiver OR, at a minimum, specific written instructions on under what conditions the patient's doctor should be contacted or the patient should go to the emergency room	Clinician	IPRO	Asthma (process)	2009	Endorsement removed *(October 2012)*		No
0052	Use of Imaging Studies for Low Back Pain	The percentage of patients with a primary diagnosis of low back pain who did not have an imaging study (plain X-ray, MRI, CT scan) within 28 days of diagnosis	Health plan, integrated delivery system	NCQA	Musculoskeletal (process)	2009	Endorsement removed *(April 2017)*	PQRS, QRUR, BPM	No
0090	Emergency Medicine: 12-Lead Electrocardiogram (ECG) Performed for Non-traumatic Chest Pain	Percentage of patients aged 40 years and older with an emergency department discharge diagnosis of non-traumatic chest pain who had a 12-lead electrocardiogram (ECG) performed	Group	AMA-PCPI	Cardiovascular (process)	2007	Endorsement removed *(December 2017)*	PQRS, QRUR, BPM	No
0092	Emergency Medicine: Aspirin at Arrival for Acute Myocardial Infarction (AMI)	Percentage of patients, regardless of age, with an emergency department discharge diagnosis of acute myocardial infarction (AMI) who had documentation of receiving aspirin within 24 h before emergency department arrival or during emergency department stay	Group, clinician	AMA-PCPI	Cardiovascular (process)	2007	Endorsement removed *(February 2016)*		No

(continued)

Table 4.1 (continued)

NQF ID	Measure title*	Measure description*	Reporting level	Measure owner*,†	Measure target (type)*	Year endorsed	Current status	CMS program‡	Relevant to cancer care?§
0093	Emergency Medicine: 12-Lead Electrocardiogram (ECG) Performed for Syncope	Percentage of patients aged 60 years and older with an emergency department discharge diagnosis of syncope who had an ECG performed	Clinician	AMA-PCPI	Cardiovascular (process)	2007	Endorsement removed *(February 2014)*		No
0094	Assessment of Oxygen Saturation for Community-Acquired Bacterial Pneumonia	Percentage of patients aged 18 years and older with the diagnosis of community-acquired bacterial pneumonia with oxygen saturation assessed	Clinician	AMA-PCPI	Pneumonia (process)	2007	Endorsement removed *(December 2011)*		No
0095	Assessment of Mental Status for Community-Acquired Bacterial Pneumonia	Percentage of patients aged 18 years and older with the diagnosis of community-acquired bacterial pneumonia with mental status assessed	Clinician	AMA-PCPI	Pneumonia (process)	2007	Endorsement removed *(December 2011)*		No
0104e	Adult Major Depressive Disorder (MDD): Suicide Risk Assessment	Percentage of patients aged 18 years and older with a diagnosis of major depressive disorder (MDD) with a suicide risk assessment completed during the visit in which a new diagnosis or recurrent episode was identified	Group, clinician	AMA-PCPI	Behavioral health (process)	2009	Endorsed	PQRS, QRUR, BPM	No
0148	Blood Cultures Performed in the Emergency Department Prior to Initial Antibiotic Received in Hospital	Percentage of pneumonia patients 18 years of age and older who have had blood cultures performed in the emergency department prior to initial antibiotic received in the hospital	Facility	CMS	Pneumonia (process)	2007	Endorsement removed *(October 2012)*		No
0151	Initial Antibiotic Received Within 6 H of Hospital Arrival	Percentage of pneumonia patients 18 years of age and older who receive their first dose of antibiotics within 6 h after arrival at the hospital	Facility	CMS	Pneumonia (process)	2009	Endorsement removed *(October 2012)*		No
0173	Emergency Department Use Without Hospitalization During the First 60 Days of Home Health	Percentage of home health stays in which patients used the emergency department but were not admitted to the hospital during the 60 days following the start of the home health stay	Facility	CMS	Care coordination (outcome)	2009	Endorsed	HACRP, HHQRP	Yes
0211	Proportion of Patients Who Died from Cancer with More Than One Emergency Department Visit in the Last 30 Days of Life	Proportion of patients who died from cancer with more than one emergency department visit in the last 30 days of life	Group	ASCO	Cancer-specific (outcome)	2009	Endorsement removed *(October 2016)*		Yes
0277	Congestive Heart Failure Rate (PQI 08)	Admissions with a principal diagnosis of heart failure per 100,000 population, ages 18 years and older	Health plan, integrated delivery system	AHRQ	Cardiovascular (process)	2007	Endorsed	MSSP	No

0286	Aspirin at Arrival	Percentage of emergency department acute myocardial infarction (AMI) patients or chest pain patients (with probable cardiac chest pain) without aspirin contraindications who received aspirin within 24 h before ED arrival or prior to transfer	Facility	CMS	Cardiovascular (process)	2007	Endorsement removed *(August 2014)*		No
0287	Median Time to Fibrinolysis	Median time from emergency department arrival to administration of fibrinolytic therapy in ED patients with ST-segment elevation or left bundle branch block (LBBB) on the electrocardiogram (ECG) performed closest to ED arrival and prior to transfer	Facility	CMS	Cardiovascular (process)	2007	Endorsement removed *(January 2012)*		No
0288	Fibrinolytic Therapy Received Within 30 Min of ED Arrival	This measure calculates the percentage of emergency department (ED) acute myocardial infarction (AMI) patients with ST-segment elevation on the electrocardiogram (ECG) closest to arrival time receiving fibrinolytic therapy during the ED stay and having a time from ED arrival to fibrinolysis of 30 min or less	Facility	CMS	Cardiovascular (process)	2007	Endorsement removed *(November 2016)*	Hospital Compare, OQR	No
0289	Median Time to ECG	Median time from emergency department arrival to ECG (performed in the ED prior to transfer) for acute myocardial infarction (AMI) or chest pain patients (with probable cardiac chest pain)	Facility	CMS	Cardiovascular (efficiency)	2007	Endorsement removed *(August 2014)*		No
0290	Median Time to Transfer to Another Facility for Acute Coronary Intervention	Median time from emergency department arrival to time of transfer to another facility for acute coronary intervention	Facility	CMS	Cardiovascular (process)	2007	Endorsed	Hospital Compare, OQR	No
0291	Emergency Transfer Communication Measure	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that required information was communicated to the receiving facility prior to departure (subsection 1) or within 60 min of transfer (subsections 2–7)	Facility	UMRHRC	Care coordination (process)	2007	Endorsed		Yes

(continued)

Table 4.1 (continued)

NQF ID	Measure title*	Measure description*	Reporting level	Measure owner*,†	Measure target (type)*	Year endorsed	Current status	CMS program‡	Relevant to cancer care?§
0292	Vital Signs	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that the entire vital signs record was communicated to the receiving facility within 60 min of departure	Facility	UMRHRC	Care coordination (process)	2007	Endorsement removed *(September 2014)*		Yes
0293	Medication Information	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that medication information was communicated to the receiving facility within 60 min of departure	Facility	UMRHRC	Care coordination (process)	2007	Endorsement removed *(September 2014)*		Yes
0294	Patient Information	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that patient information was communicated to the receiving facility within 60 min of departure	Facility	UMRHRC	Care coordination (process)	2007	Endorsement removed *(September 2014)*		Yes
0295	Physician Information	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that physician information was communicated to the receiving facility within 60 min of departure	Facility	UMRHRC	Care coordination (process)	2007	Endorsement removed *(September 2014)*		Yes
0296	Nursing Information	Percentage of patients transferred to another healthcare facility whose medical record documentation indicated that nursing information was communicated to the receiving facility within 60 min of departure	Facility	UMRHRC	Care coordination process)	2007	Endorsement removed *(September 2014)*		Yes
0297	Procedures and Tests	Patients who are transferred from an ED to another healthcare facility have communicated with the receiving facility within 60 min of discharge a list of tests done and results sent	Facility	UMRHRC	Care coordination (process)	2007	Endorsement removed *(September 2014)*		Yes
0489	The Ability for Providers with HIT to Receive Laboratory Data Electronically Directly into Their Qualified/Certified EHR System as Discrete Searchable Data Elements	Documents the extent to which a provider uses certified/qualified electronic health record (EHR) system that incorporates an electronic data interchange with one or more laboratories allowing for direct electronic transmission of laboratory data into the EHR as discrete searchable data elements	Facility	CMS	Care coordination (structure)	2008	Endorsement removed *(April 2014)*		Yes

0491	Tracking of Clinical Results Between Visits	Documentation of the extent to which a provider uses a certified/qualified electronic health record (EHR) system to track pending laboratory tests, diagnostic studies (including common preventive screenings), or patient referrals	Facility	CMS	Care coordination (structure)	2008	Endorsement removed *(April 2014)*		Yes
0495	Median Time from ED Arrival to ED Departure for Admitted ED Patients	Median time from emergency department arrival to time of departure from the emergency room for patients admitted to the facility from the emergency department	Facility	CMS	Care coordination (process)	2008[‖,¶]	Endorsement removed *(November 2018)*	Hospital Compare, IQR	Yes
0496	Median Time from ED Arrival to ED Departure for Discharged ED Patients	Median time from emergency department arrival to time of departure from the emergency room for patients discharged from the emergency department (ED)	Facility	CMS	Care coordination (process)	2008[‖,¶]	Endorsement removed *(October 2018)*	Hospital Compare, OQR	Yes
0497	Admit Decision Time to ED Departure Time for Admitted Patients	Median time from admit decision time to time of departure from the emergency department for emergency department patients admitted to inpatient status	Facility	CMS	Care coordination (process)	2008[‖,¶]	Endorsement removed *(November 2018)*	Hospital Compare, IQR	Yes
0498	Door to Diagnostic Evaluation by a Qualified Medical Personnel	Time of first contact in the ED to the time when the patient sees qualified medical personnel for patient evaluation and management	Facility, clinician	LSU	Care coordination (other)	2008[‖,¶]	Endorsement removed *(May 2012)*		Yes
0499	Left Without Being Seen	Percent of patients leaving without being seen by a qualified medical personnel	Facility, clinician	LSU	Care coordination (other)	2008	Endorsement removed *(May 2012)*		Yes
0500	Severe Sepsis and Septic Shock: Management Bundle	This measure focuses on adults 18 years and older with a diagnosis of severe sepsis or septic shock. Consistent with Surviving Sepsis Campaign guidelines, the measure contains several elements, including measurement of lactate, obtaining blood cultures, administering broad-spectrum antibiotics, fluid resuscitation, vasopressor administration, reassessment of volume status and tissue perfusion, and repeat lactate measurement	Facility	HFH	Composite	2008	Endorsed		Yes

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Table 4.1 (continued)

NQF ID	Measure title*	Measure description*	Reporting level	Measure owner*,†	Measure target (type)*	Year endorsed	Current status	CMS program‡	Relevant to cancer care?§
0501	Confirmation of Endotracheal Tube Placement	Any time an endotracheal tube is placed into a patient's airway in the emergency department (ED) or a patient arrives to the ED with an endotracheal tube already in place (via EMS or hospital transfer), there should be appropriate confirmation of ETT placement and documentation of its performance in the medical record	Population, integrated delivery system, facility, group, clinician	CCF	Pulmonary (process)	2008‖,¶	Endorsement removed *(June 2012)*		No
0502	Pregnancy Test for Female Abdominal Pain Patients	Percentage of female patients aged 14 to 50 who present to the emergency department (ED) with a chief complaint of abdominal pain for whom a pregnancy test ordered	Facility, group, clinician	ACEP	Perinatal (process)	2008‖,¶	Endorsement removed *(May 2012)*		No
0503	Anticoagulation for Acute Pulmonary Embolus Patients	Number of acute embolus patients who have orders for anticoagulation (heparin or low-molecular-weight heparin) for pulmonary embolus while in the ED	Facility, group, clinician	ACEP	Cardiovascular (process)	2008‖,¶	Endorsement removed *(January 2013)*		No
0504	Pediatric Weight Documented in Kilograms	Percentage of emergency department visits by patients <18 years of age with a current weight documented in kilograms in the ED electronic health record; measure to be reported each month	Facility	AAP	Safety (process)	2008‖,¶	Endorsement removed *(January 2013)*		No
0514	MRI Lumbar Spine for Low Back Pain		Population, facility	CMS	Musculoskeletal (process)		Endorsement removed *(April 2017)*	Hospital Compare, OQR	No
0549	Pharmacotherapy Management of COPD Exacerbation (PCE)	This measure assesses the percentage of COPD exacerbations for members 40 years of age and older who had an acute inpatient discharge or ED encounter on or between January 1 and November 30 of the measurement year and who were dispensed appropriate medications	Population, health plan, integrated delivery system, facility, group, clinician	NCQA	COPD (process)	2009	Endorsement removed *(July 2012)*		No
0604	Adult(s) with Diabetes Mellitus that Had a Serum Creatinine in the Last 12 Reported Months	This measure identifies adults with diabetes mellitus that had a serum creatinine test in the last 12 reported months	Population, health plan, integrated delivery system, facility, group, clinician	Optum	Endocrine (process)	2009	Endorsement removed *(December 2013)*		No

0605	Patient(s) with Hypertension that Had a Serum Creatinine in the Last 12 Reported Months	This measure identifies patients with hypertension (HTN) who had a serum creatinine in the last 12 reported months	Population, health plan, integrated delivery system, facility, group, clinician	Optum	Cardiovascular (process)	2009	Endorsement removed *(December 2013)*		No
0644	Patients with a Transient Ischemic Event ER Visit that Had a Follow-Up Office Visit	Patient(s) with a recent emergency room encounter for a transient cerebral ischemic event that had any physician visit within 14 days of the acute event	Population, health plan, integrated delivery system, facility, group, clinician	Optum	Stroke (process)	2010	Endorsement removed *(March 2013)*		No
0649	Transition Record with Specified Elements Received by Discharged Patients (Emergency Department Discharges to Ambulatory Care [Home/Self-Care] or Home Health Care)	Percentage of discharges from an emergency department (ED) to ambulatory care or home healthcare, in which the patient, regardless of age, or their caregiver(s), received a transition record at the time of ED discharge including, at a minimum, all of the specified elements	Integrated delivery system, facility	AMA-PCPI	Care coordination (process)	2010	Endorsement removed *(July 2017)*		Yes
0652	Rh immunoglobulin (Rhogam) for Rh-negative pregnant women at risk of fetal blood exposure	Percent of Rh-negative pregnant women at risk of fetal blood exposure who receive Rhogam in the ED	Group, clinician	ACEP	Perinatal (process)	2011	Endorsement removed *(July 2014)*		No
0660	Troponin Results for Emergency Department Acute Myocardial Infarction (AMI) Patients or Chest Pain Patients (with Probable Cardiac Chest Pain) Received Within 60 min of Arrival	Emergency department acute myocardial infarction (AMI) patients or chest pain patients (with probable cardiac chest pain) with an order for troponin during the stay and having a time from ED arrival to completion of troponin results within 60 min of arrival	Facility	CMS	Cardiovascular (process)	2011	Endorsement removed *(November 2012)*		No
0661	Head CT or MRI Scan Results for Acute Ischemic Stroke or Hemorrhagic Stroke Patients Who Received Head CT or MRI Scan Interpretation Within 45 Min of ED Arrival	This measure calculates the percentage of acute ischemic stroke or hemorrhagic stroke patients who arrive at the ED within 2 h of the onset of symptoms and have a head computed tomography (CT) or magnetic resonance imaging (MRI) scan interpreted within 45 min of ED arrival	Facility	CMS	Stroke (process)	2011	Endorsed	Hospital Compare, OQR	No
0662	Median Time to Pain Management for Long Bone Fracture	Median time from emergency department arrival to time of initial oral or parenteral pain medication administration for emergency department patients with a principal diagnosis of long bone fracture (LBF)	Facility	CMS	Musculoskeletal (process)	2011	Endorsement removed *(January 2015)*	Hospital Compare, OQR	No

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Table 4.1 (continued)

NQF ID	Measure title*	Measure description*	Reporting level	Measure owner*,†	Measure target (type)*	Year endorsed	Current status	CMS program‡	Relevant to cancer care?§
0664	Patient(s) with an Emergency Medicine Visit for Syncope that Had an ECG	This measure identifies patients with an emergency medicine visit for syncope that had an ECG done as part of their evaluation	Population, health plan, integrated delivery system, facility, group, clinician	Optum	Cardiovascular (process)	2011	Endorsement removed *(December 2013)*		No
0665	Patient(s) with an Emergency Medicine Visit for Non-traumatic Chest Pain that Had an ECG	This measure identifies patients with an emergency medicine visit for non-traumatic chest pain that had an ECG done as part of their evaluation	Population, health plan, integrated delivery system, facility, group, clinician	Optum	Cardiovascular (process)	2011	Endorsement removed *(December 2013)*		No
0666	Ultrasound Guidance for Internal Jugular Central Venous Catheter Placement	Percent of adult patients aged 18 years and older with an internal jugular central venous catheter placed in the emergency department (ED) under ultrasound guidance	Group, clinician	ACEP	Pulmonary (process)	2011	Endorsement removed *(May 2017)*		No
0667	Inappropriate Pulmonary CT Imaging for Patients at Low Risk for Pulmonary Embolism	Percent of patients undergoing CT pulmonary angiogram for the evaluation of possible PE who are at low-risk for PE consistent with guidelines(1, 2) prior to CT imaging	Facility, group	ACEP	Pulmonary (efficiency)	2011	Endorsement removed *(February 2016)*		No
0705	Proportion of Patients Hospitalized with Stroke that Have a Potentially Avoidable Complication (During the Index Stay or in the 30-Day Post-discharge Period)	Percent of adult population aged 18–65 years who were admitted to a hospital with stroke, were followed for 1 month after discharge, and had one or more potentially avoidable complications (PACs)	Population, health plan, facility, group	HCI3	Stroke (outcome)	2011	Endorsement removed *(December 2015)*		No
0722	Pediatric Symptom Checklist (PSC)	The Pediatric Symptom Checklist (PSC) is a brief parent-report questionnaire that is used to assess overall psychosocial functioning in children from 3 to 18 years of age	Population, health plan, integrated delivery system, facility, group, clinician	MGH	Behavioral health (outcome)		Endorsement removed *(March 2015)*		No
1381	Asthma Emergency Department Visits	Percentage of patients with asthma who have greater than or equal to one visit to the emergency room for asthma during the measurement period	Population, health plan	ALMA	Asthma (outcome)	2011	Endorsement removed *(February 2014)*		No

1598	Total Resource Use Population-Based PMPM Index	The Resource Use Index (RUI) is a risk-adjusted measure of the frequency and intensity of services utilized to manage a provider group's patients. Resource use includes all resources associated with treating members including professional, facility inpatient and outpatient, pharmacy, lab, radiology, ancillary, and behavioral health services	Population, group	HealthPartners	Care coordination (cost/resource use)	2012	Endorsed		Yes
1604	Total Cost of Care Population-Based PMPM Index	Total Cost of Care reflects a mix of complicated factors such as patient illness burden, service utilization, and negotiated prices. Total Cost Index (TCI) is a measure of a primary care provider's risk-adjusted cost-effectiveness at managing the population they care for	Population, group	HealthPartners	Care coordination (cost/resource use)	2012	Endorsed		Yes
1609	ETG-Based Hip/Knee Replacement Cost of Care Measure	The measure focuses on resources used to deliver episodes of care for patients who have undergone a hip/knee replacement	Population, health plan, integrated delivery system, facility, group, clinician	Optum	Musculoskeletal (cost/resource use)	2012	Endorsement removed *(July 2018)*		No
1611	ETG-Based Pneumonia Cost of Care Measure	The measure focuses on resources used to deliver episodes of care for patients with pneumonia	Population, health plan, integrated delivery system, facility, group, clinician	Optum	Pneumonia (cost/resource use)	2012	Endorsement removed *(December 2014)*		Yes
1716	National Healthcare Safety Network (NHSN) Facility-Wide Inpatient Hospital-Onset Methicillin-Resistant *Staphylococcus aureus* (MRSA) Bacteremia Outcome Measure	Standardized infection ratio (SIR) and adjusted ranking metric (ARM) of hospital-onset unique blood source MRSA laboratory-identified events (LabID events) among all inpatients in the facility	Population, facility	CDC	Infectious disease (outcome)	2012	Endorsed	Hospital Compare, IQR, VBP, HACRP, IRF QRP, LTCH QRP, PCHQR	Yes
1717	National Healthcare Safety Network (NHSN) Facility-Wide Inpatient Hospital-Onset *Clostridium difficile* Infection (CDI) Outcome Measure	Standardized infection ratio (SIR) and adjusted ranking metric (ARM) of hospital-onset CDI laboratory-identified events (LabID events) among all inpatients in the facility, excluding well-baby nurseries and neonatal intensive care units (NICUs)	Population, facility	CDC	Infectious disease (outcome)	2012	Endorsed	Hospital Compare, IQR, VBP, HACRP, IRF QRP, LTCH QRP, PCHQR	Yes

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Table 4.1 (continued)

NQF ID	Measure title*	Measure description*	Reporting level	Measure owner*,†	Measure target (type)*	Year endorsed	Current status	CMS program‡	Relevant to cancer care?§
1799	Medication Management for People with Asthma	The percentage of patients 5–64 years of age during the measurement year who were identified as having persistent asthma and were dispensed appropriate medications that they remained on during the treatment period. Two rates are reported. 1. The percentage of patients who remained on an asthma controller medication for at least 50% of their treatment period 2. The percentage of patients who remained on an asthma controller medication for at least 75% of their treatment period	Health plan, integrated delivery system	NCQA	Asthma (process)	2015	Endorsement removed *(August 2016)*		No
1800	Asthma Medication Ratio	The percentage of patients 5–64 years of age who were identified as having persistent asthma and had a ratio of controller medications to total asthma medications of 0.50 or greater during the measurement year	Health plan, integrated delivery system	NCQA	Asthma (process)	2012	Endorsed		No
1824	L1A: Screening for Preferred Spoken Language for Healthcare	This measure is used to assess the percent of patient visits and admissions where preferred spoken language for healthcare is screened and recorded	Facility, group	GWU	Disparities (process)	2012	Endorsement removed *(April 2017)*		Yes
2505	Emergency Department Use Without Hospital Readmission During the First 30 Days of Home Health	Percentage of home health stays in which patients who had an acute inpatient hospitalization in the 5 days before the start of their home health stay used an emergency department but were not admitted to an acute care hospital during the 30 days following the start of the home health stay	Facility	CMS	Care coordination (outcome)	2014	Endorsement removed *(June 2020)*		No
2539	Facility 7-Day Risk-Standardized Hospital Visit Rate After Outpatient Colonoscopy	Rate of risk-standardized, all-cause, unplanned hospital visits within 7 days of an outpatient colonoscopy among Medicare fee-for-service (FFS) patients aged 65 years and older	Facility	CMS	Gastrointestinal (outcome)	2014	Endorsed	ASCQR, Hospital Compare, OQR	Yes
2548	Child Hospital Consumer Assessment of Healthcare Providers and Systems (Child HCAHPS) Survey	The Child Hospital Consumer Assessment of Healthcare Providers and Systems (Child HCAHPS) survey is a standardized survey instrument that asks parents and guardians (henceforth referred to as parents) of children under 18 years old to report on their and their child's experiences with inpatient hospital care	Facility	AHRQ	Pediatric (outcome)	2015	Endorsed		Yes

2605	Follow-Up After Emergency Department Visit for Mental Illness or Alcohol and Other Drug Abuse or Dependence	The percentage of discharges for patients 18 years of age and older who had a visit to the emergency department with a primary diagnosis of mental health or alcohol or other drug dependence during the measurement year *and* who had a follow-up visit with any provider with a corresponding primary diagnosis of mental health or alcohol or other drug dependence within 7 and 30 days of discharge	Population, health plan	NCQA	Behavioral health (process)	2015	Endorsed		No
2687	Hospital Visits After Hospital Outpatient Surgery	Facility-level, postsurgical risk-standardized hospital visit ratio (RSHVR) of the predicted to expected number of all-cause, unplanned hospital visits within 7 days of a same-day surgery at a hospital outpatient department (HOPD) among Medicare fee-for-service (FFS) patients aged 65 years and older	Facility	CMS	Surgery (outcome)	2015	Endorsed		Yes
2689	Ambulatory Care Sensitive Emergency Department Visits for Dental Caries in Children	Number of emergency department visits for caries-related reasons per 100,000 member months for all enrolled children	Integrated delivery system	ADA	Dental (outcome)	2015	Endorsed		No
2695	Follow-Up After Emergency Department Visits for Dental Caries in Children	Percentage of ambulatory care sensitive emergency department (ED) visits for dental caries among children 0–20 years in the reporting period for which the member visited a dentist within (a) 7 days and (b) 30 days of the ED visit	Integrated delivery system	ADA	Dental (process)	2015	Endorsed		No
2723	Wrong-Patient Retract-and-Reorder (Wrong Patient-RAR) Measure	A Wrong-Patient Retract-and-Reorder (Wrong Patient-RAR) event occurs when an order is placed on a patient within an EHR, and is retracted within 10 min, and then the same clinician places the same order on a different patient within the next 10 min	Integrated delivery system, facility, group	NYPH	Safety (outcome)	2015	Endorsed		Yes
2806	Pediatric Psychosis: Screening for Drugs of Abuse in the Emergency Department	Percentage of children/adolescents aged 5 to 19 years old seen in the emergency department with psychotic symptoms who are screened for alcohol or drugs of abuse	Facility	SCRI	Behavioral health (process)	2016	Endorsed		No

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Table 4.1 (continued)

NQF ID	Measure title*	Measure description*	Reporting level	Measure owner*,†	Measure target (type)*	Year endorsed	Current status	CMS program‡	Relevant to cancer care?§
2863	CSTK-06: Nimodipine Treatment Administered	Proportion of subarachnoid hemorrhage (SAH) patients aged 18 years and older for whom nimodipine treatment was administered within 24 h of arrival at this hospital	Facility	TJC	Stroke (process)	2016	Endorsed		No
2864	CSTK-01: National Institutes of Health Stroke Scale (NIHSS) Score Performed for Ischemic Stroke Patients	Proportion of ischemic stroke patients aged 18 years or older for whom an initial NIHSS score is performed prior to any acute recanalization therapy (i.e., intravenous (IV) thrombolytic (t-PA) therapy, or intra-arterial (IA) thrombolytic (t-PA) therapy, or mechanical endovascular reperfusion (MER) therapy) in patients undergoing recanalization therapy and documented in the medical record, or documented within 12 h of arrival at the hospital emergency department in patients who do not undergo recanalization therapy	Facility	TJC	Stroke (process)	2016	Endorsed		No
2866	CSTK-03: Severity Measurement Performed for Subarachnoid Hemorrhage (SAH) and Intracerebral Hemorrhage (ICH) Patients (Overall Rate)	Proportion of SAH and ICH stroke patients aged 18 years or older for whom a severity measurement (i.e., Hunt and Hess Scale for SAH patients or ICH Score for ICH patients) is performed prior to surgical intervention (e.g., clipping, coiling, or any surgical intervention) in patients undergoing surgical intervention and documented in the medical record, *or* documented within 6 h of arrival at the hospital emergency department in patients who do not undergo surgical intervention	Facility	TJC	Stroke (process)	2016	Endorsed		No
2880	Excess Days in Acute Care (EDAC) After Hospitalization for Heart Failure (HF)	The measure assesses days spent in acute care within 30 days of discharge from an inpatient hospitalization for HF to provide a patient-centered assessment of the post-discharge period	Facility	CMS	Cardiovascular (outcome)	2016	Endorsed		No
2881	Excess Days in Acute Care (EDAC) After Hospitalization for Acute Myocardial Infarction (AMI)	This measure assesses days spent in acute care within 30 days of discharge from an inpatient hospitalization for acute myocardial infarction (AMI) to provide a patient-centered assessment of the post-discharge period	Facility	CMS	Cardiovascular (outcome)	2016	Endorsed		No

2882	Excess Days in Acute Care (EDAC) After Hospitalization for Pneumonia	This measure assesses days spent in acute care within 30 days of discharge from an inpatient hospitalization for pneumonia, including aspiration pneumonia or for sepsis (not severe sepsis) with a secondary discharge diagnosis of pneumonia coded in the claim as present on admission (POA) and no secondary diagnosis of severe sepsis coded as POA	Facility	CMS	Pulmonary (outcome)	2016	Endorsed		Yes
2983e	Potassium Sample Hemolysis in the Emergency Department	Percentage of laboratory potassium samples drawn in the emergency department (ED) with hemolysis	Facility	CCF	Safety (outcome)	2017	Approved for trial use (5)		Yes
3309	Risk-Standardized Survival Rate (RSSR) for Inhospital Cardiac Arrest	This measure estimates a hospital -level risk standardized survival rate (RSSR) for patients aged 18 years and older who experience an inhospital cardiac arrest	Facility	AHA	Cardiovascular (Outcome)	2019	Endorsed		No
3316e	Safe Use of Opioids—Concurrent Prescribing	Patients aged 18 years and older prescribed two or more opioids or an opioid and benzodiazepine concurrently at discharge from a hospital-based encounter (inpatient or emergency department [ED], including observation stays)	Facility	CMS	Safety (process)	2018	Endorsed		No
3357	Facility-Level 7-Day Hospital Visits After General Surgery Procedures Performed at Ambulatory Surgical Centers	Facility-level risk-standardized ratio of acute, unplanned hospital visits within 7 days of a general surgery procedure performed at an ambulatory surgical center (ASC) among Medicare fee-for-service (FFS) patients aged 65 years and older	Facility	CMS	Surgery (outcome)	2018	Endorsed		Yes
3366	Hospital Visits After Urology Ambulatory Surgical Center Procedures	Facility-level risk-standardized rate of acute, unplanned hospital visits within 7 days of a urology procedure performed at an ambulatory surgical center (ASC) among Medicare fee-for-service (FFS) patients aged 65 years and older	Facility	CMS	Urology (outcome)	2019	Endorsed		Yes
3400	Use of Pharmacotherapy for Opioid Use Disorder (OUD)	The percentage of Medicaid beneficiaries ages 18–64 with an OUD who filled a prescription for or were administered or dispensed an FDA-approved medication for the disorder during the measure year	Population	CMS	Safety (process)	2018	Endorsed		No

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Table 4.1 (continued)

NQF ID	Measure title*	Measure description*	Reporting level	Measure owner*,†	Measure target (type)*	Year endorsed	Current status	CMS program‡	Relevant to cancer care?§
3453	Continuity of Care After Inpatient or Residential Treatment for Substance Use Disorder (SUD)	Percentage of discharges from an inpatient or residential treatment for substance use disorder (SUD) for Medicaid beneficiaries, ages 18 to 64, which was followed by a treatment service for SUD	Population	CMS	Safety (process)	2019	Endorsed		No
3455	Timely Follow-Up After Acute Exacerbations of Chronic Conditions	The percentage of issuer-product-level acute events requiring either an emergency department (ED) visit or hospitalization for one of the following six chronic conditions: hypertension, asthma, heart failure (HF), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), or diabetes mellitus (Type I or Type II), where follow-up was received within the timeframe recommended by clinical practice guidelines in a nonemergency outpatient setting	Health plan	IMPAQ	Care coordination (process)	2019	Endorsed		No
3470	Hospital Visits After Orthopedic Ambulatory Surgical Center Procedures	Facility-level risk-standardized rate of acute, unplanned hospital visits within 7 days of an orthopedic procedure performed at an ambulatory surgical center (ASC) among Medicare fee-for-service (FFS) patients aged 65 years and older	Facility	CMS	Musculoskeletal (outcome)	2019	Endorsed		Yes
3488	Follow-Up After Emergency Department Visit for Alcohol and Other Drug Abuse or Dependence	The percentage of emergency department (ED) visits for members 13 years of age and older with a principal diagnosis of alcohol or other drug (AOD) abuse or dependence, who had a follow-up visit for AOD	Health plan	NCQA	Behavioral health (process)	2019	Endorsed		No
3489	Follow-Up After Emergency Department Visit for Mental Illness	The percentage of emergency department (ED) visits for members 6 years of age and older with a principal diagnosis of mental illness or intentional self-harm, who had a follow-up visit for mental illness	Health plan	NCQA	Behavioral health (process)	2019	Endorsed		No

3490	Admission and Emergency Department (ED) Visits for Patients Receiving Outpatient Chemotherapy	The Admission and Emergency Department (ED) Visits for Patients Receiving Outpatient Chemotherapy Measure, hereafter referred to as the chemotherapy measure, estimates hospital-level, risk-adjusted rates of inpatient admissions or ED visits for cancer patients =18 years of age for at least one of the following diagnoses—anemia, dehydration, diarrhea, emesis, fever, nausea, neutropenia, pain, pneumonia, or sepsis—within 30 days of hospital-based outpatient chemotherapy treatment	Facility	CMS	Cancer-specific (outcome)	2019	Endorsed		Yes

Source: This table is based on the authors' analysis of ED quality measures that are currently endorsed or were previously endorsed by the NQF, including measures currently used in CMS reporting programs [218]

Note:

*The measure titles, descriptions, and owners in this table are based on the information listed on the NQF website. These fields may differ from the measure titles, descriptions, and owners when the measures were initially endorsed by the NQF. Furthermore, a measure's use in CMS programs may have changed since the NQF website was last updated (e.g., measures reported under PQRS may now be part of MIPS)

†Measure owners are as follows: AAP, American Academy of Pediatrics (www.aap.org); ACEP, American College of Emergency Physicians (www.ada.org/en); ADA, American Dental Association (www.acep.org); AHA, American Heart Association (www.heart.org); AHRQ, Agency for Healthcare Research and Quality (www.ahrq.org); ALMA, Alabama Medicaid Agency (www.medicaid.alabama.gov); AMA-PCPI, American Medical Association-Physician Consortium for Performance Improvement (www.ama-assn.org/ama/home.page); ASCO, American Society of Clinical Oncologic (www.asco.org); CCF, Cleveland Clinic Foundation (my.clevelandclinic.org); CDC, Centers for Disease Control and Prevention (www.cdc.gov); CMS, Centers for Medicare & Medicaid Services (www.cms.gov); CMS, Centers for Medicare & Medicaid Services (www.cms.gov); HCI3, Health Care Incentives Improvement Institute (www.hci3.org); HealthPartners (www.healthpartners.com/provider-public); HFH, Henry Ford Hospital (www.henryford.com/homepage_hfh.cfm?id=37471); IMPAQ, IMPAQ International (www.impaqint.com); IPRO (www.ipro.org); LSU, Louisiana State University (www.lsuhospitals.org); NCQA, National Committee for Quality Assurance (www.ncqa.org); MGH, Massachusetts General Hospital (www.massgeneral.org); NYPH, New York-Presbyterian Hospital (www.nyp.org); Optum (www.optum.com); Optum (www.optum.com); TJC, The Joint Commission (www. Jointcommission.org/en); UMRHRC, University of Minnesota Rural Health Research Center (rhrc.umn.edu)

‡CMS public reporting programs are as follows: ASCQR, Ambulatory Surgical Center Quality Reporting (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/ASC-Quality-Reporting); HACRP, Hospital-Acquired Condition Reduction Program (www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/HAC-Reduction-Program); HHQRP, Home Health Quality Reporting Program (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HomeHealthQualityInits); HHVBP, Home Health Value-Based Purchasing (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Value-Based-Programs/Other-VBPs/HHVBP); Hospital Compare (www.medicare.gov/hospitalcompare/search.html); IQR, Inpatient Quality Reporting (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/HospitalRHQDAPU.html); IRF QRP, Inpatient Rehabilitation Facility Quality Reporting Program (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/IRF-Quality-Reporting); LTCQRP, Long-Term Care Hospital Quality Reporting (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/LTCH-Quality-Reporting); MSSP, Medicare Shared Savings Program (www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/sharedsavingsprogram); OQR, Outpatient Quality Reporting (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/HospitalOutpatientQualityReportingProgram.html); PCHQR, PPS-Exempt Cancer Hospitals Quality Reporting Program (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/PCHQR); PQRS, Physician Quality Reporting System (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/PQRS/index.html); QHP QRS, Qualified Health Plan Quality Rating System (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/QualityInitiativesGenInfo/ACA-MQI/Quality-Rating-System/About-the-QRS); QRUR, Quality and Resource Use Reports (www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeedbackProgram/2016-QRUR); QRUR, Quality and Resource Use Reports (www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeedbackProgram/2016-QRUR); VBP, Value-Based Purchasing (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Value-Based-Programs/HVBP/Hospital-Value-Based-Purchasing)

§Relevance to cancer care is based on the authors' analysis of the measure specifications. Some measures (e.g., NQF #0090-Emergency Medicine: 12-Lead Electrocardiogram (ECG) Performed for Non-traumatic Chest Pain) may apply to cancer patients with other comorbidities as well as health status changes. However, the measures are not directly relevant to cancer care

‖Measure was approved for trial use by NQF. NQF's Trial Use Program enables temporary use of electronic measures, or eMeasures, that lack full reliability and validity testing but are otherwise ready for implementation [218]

¶Measure was given time-limited endorsement. Time-limited endorsement is granted to measures that meet NQF evaluation criteria, but have not been adequately field-tested. Measure developers are given up to 2 years to demonstrate the reliability, validity, and feasibility of the measure based on testing at multiple provider sites [219]

including the IQR program and PPS-Exempt Cancer Hospitals Quality Reporting Program (PCHQR). Over time, many of these measures have been retired from federal reporting programs or are no longer endorsed by the NQF. As of July 2020, there are 39 NQF-endorsed ED quality measures, including 9 ED quality measures used in CMS reporting programs. One additional ED quality measure has been approved for trial use (see Table 4.1). ED measures relevant to cancer care and the limitations of those measures are summarized in the following section and in Table 4.2.

Table 4.2 Existing ED measures relevant to cancer care, current gaps, and measure development priorities

Cancer-specific ED measures
Description: Measure aspects of emergency care that are unique to cancer patients. Include measures of the processes, outcomes, structure, efficiency, and costs of care as well as patients' perception-of-care
Rationale: Cancer patients visit the ED throughout the continuum of care and often present with complex, interrelated symptom burden (particularly at the end of life). Many ED measures focus on cardiovascular disease and are not relevant to oncologic emergency care. In addition, many cancer patients experience unique quality of care issues (e.g., late-stage cancers presenting to the ED) that reflect quality issues in other care settings and are not captured in existing measures. Widespread adoption of cancer-specific ED measures will help stimulate improvements in emergency oncologic care
Current measures: Two cancer-specific ED measures have been developed, and one measure is currently National Quality Forum (NQF)-endorsed. They assess overutilization of ED services, due to poor symptom management, aggressive treatment, poor care coordination, or inadequate access to care
Examples:
– NQF measure #3490—Admission and Emergency Department (ED) Visits for Patients Receiving Outpatient Chemotherapy
Health services research priorities: *Listed below by measure type*
Measure development priorities: *Listed below by measure type*
ED outcome measures
Description: Measure the outcomes of emergency care, including the sustainability of health post-ED discharge, timeliness of ED care, and treatment complications during and after ED discharge
Rationale: Cancer patients frequently visit the ED for symptom management (e.g., management of acute pain and fatigue) due to cancer treatment or cancer progression. In addition, ED care delays are associated with ED overcrowding and boarding and, ultimately, poorer outcomes and compromised quality of life. Failure to measure the timeliness of care—in particular, timely symptom improvement—represents a failure to measure the most important outcomes for these patients
Current measures: There are 17 NQF-endorsed ED outcome measures; these measures largely assess overutilization of ED services and patient safety
Examples:
– NQF measure #2882—Excess days in acute care (EDAC) after hospitalization for pneumonia
– NQF measure #3309—Risk-Standardized Survival Rate (RSSR) for Inhospital Cardiac Arrest
Health services research priorities:
– Develop protocols to adopt validated patient-reported outcome surveys as a standard of care for EDs to collect data on symptom burden and quality of life in the ED and post-ED discharge. Focus on minimizing patient burden and leveraging telehealth and other emerging technologies, where possible
– Study clinical and patient characteristics that are associated with repeat ED visits and post-ED discharge health decline in the cancer population
Measure development priorities:
– "Time to" patient-reported symptom improvement in the ED, stratified by chief complaint
– "Time to" cancer diagnosis, for patients presenting to the ED with an undiagnosed cancer
– Sustainability of patient-reported symptom improvement post-ED discharge, stratified by chief complaint
– Repeat ED visits within 2, 7, and 14 days of ED discharge, stratified by chief complaint
– ED length of stay for cancer patients, stratified by (1) patients admitted to an inpatient unit, (2) patients transferred to another facility, and (3) patients discharged home
ED process measures
Description: Assess compliance with established standards of ED care that have been linked to improved patient outcomes, fewer unnecessary services, and more equitable care. Include a wide array of measures, such as adherence to guideline-based diagnostic testing and treatment; protocols around patient intake, discharge, and care coordination; and policies to ensure equitable care for vulnerable patient populations
Rationale: Routine measurement of adherence to guideline-based care can highlight practice variations that contribute to poorer outcomes and higher costs of care. Measuring care coordination by ED providers is important to ensure that patients are guided to appropriate follow-up care and to prevent repeat ED visits and inpatient admissions
Current measures: There are 19 NQF-endorsed ED process measures. Fourteen of these measures are condition- or population-specific; several measures focus on substance use disorder. Two ED process measures evaluate care coordination for patients discharged to outpatient care
Examples:
– NQF measure #0004—Initiation and Engagement of Alcohol and Other Drug Abuse or Dependence Treatment
– NQF measure #0291—Emergency Transfer Communication Measure

Table 4.2 (continued)

Health services research priorities:
– Develop algorithms to identify patients at potential risk of presenting to the ED with an undiagnosed cancer
– Test methods to promote care coordination between outpatient oncologic and ED providers
– Model episodes of oncologic emergency care, with well-defined endpoints and treatment pathways
– Develop algorithms to identify patients at risk for disparities in care that present to the ED
Measure development priorities:
– Screening and diagnosis for high-frequency complications that present to the ED (e.g., pain, fatigue, dyspnea, nausea, dehydration, depression, and cognitive impairment)
– Patients discharged with a referral to an appropriate outpatient oncologic provider
– Advance care planning discussions for patients with advanced cancer
– Cancers diagnosed in the ED, stratified by (1) cancer type and (2) stage of disease
ED cost /resource use measures
Description: Calculate direct and indirect costs (or assess resource utilization) for a specific healthcare service, episode of care, or medical condition. Demonstrate variations in costs across geographic regions, medical conditions, care delivery settings, and providers
Rationale: Cost and resource use measures can increase transparency around cost inefficiencies (perceived and actual), higher costs associated with adverse events, delayed diagnosis and treatment, and individual patient factors, such as comorbid conditions. Furthermore, these measures can provide important insights into cost variation between providers, care delivery settings, and geographic regions, among patients with similar diagnoses, and across the continuum of cancer care
Current measures: There are two NQF-endorsed cost/resource use measures that are relevant to ED care
Examples
– NQF measure #1598—Total Resource Use Population-Based PMPM Index
– NQF measure #1604—Total Cost of Care Population-Based PMPM Index
Health services research priorities:
– Model episodes of oncologic emergency care, with well-defined endpoints and treatment pathways
Measure development priorities:
– Costs of care per ED visit, stratified by chief complaint
– Cost of diagnosing asymptomatic or quasi-symptomatic cancers in the ED
– Costs of managing patient comorbidities in the ED
– Costs of care by adverse event
– Costs of ED care in the last 7, 14, and 30 days of life
ED efficiency measures
Description: Examine the relationship between inputs and outputs in emergency care; they compare resource use (and associated costs) with the level of health outcome achieved
Rationale: Significant resources are expended in managing the complex—and often interrelated—symptoms, comorbidities, and psychosocial needs of patients presenting to the ED, particularly cancer patients
Current measures: There are no NQF-endorsed ED efficiency measures
Examples: None
Health services research priorities:
– Understand the overuse, underuse, and misuse of ED resources in cancer patients; this is largely unstudied beyond the frequency of ED visits. Develop guidelines for appropriate ED resource utilization for cancer patients
– Evaluate the relationship between ED resource utilization and outcomes for cancer patients
– Study the relationship between resource utilization (in the ED and in the outpatient setting) and repeat ED visits for cancer patients. Develop protocols to reduce repeat ED visits for cancer patients, particularly at the end of life
Measure development priorities:
– Efficient utilization of advanced imaging studies for cancer patients
ED patients' perception-of-care measures
Description: Evaluate patients' satisfaction or experience with the healthcare received
Rationale: While restoration of health is of primary importance among cancer patients, equally important is patient (and caregiver) experience with care throughout the cancer care continuum. This is particularly true for patients with advanced cancer whose treatment may be noncurative.
Current measures: One ED patients' perception-of-care survey has been developed, but it is not NQF-endorsed or used in public reporting programs. The Child Hospital Consumer Assessment of Healthcare Providers and Systems (Child HCAHPS) Survey is NQF-endorsed but classified as an outcome measure
Examples:
– Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey for emergency care (ED CAHPS)
Health services research priorities:
– Strategies to address the psychosocial needs of cancer patients with advanced disease and their caregivers
Measure development and research priorities:
– Relevance of the ED CAHPS survey to oncologic emergency medicine
– Survey of caregiver experience with emergency care and overall caregiver burden

Source: This table is based on the authors' analysis of NQF-endorsed ED measures relevant to cancer care [220], current gaps, and measure development priorities as of July 2020

Limitations of Existing Quality Measures for Emergency Departments

Despite the noteworthy efforts to date, the current ED performance measurement landscape has substantial limitations. For example, several ED measures are reported on Hospital Compare. However, these measures are largely provider-oriented, reflect fragmented care delivery, and lack a clear method to address upstream care delivery challenges that often present in the ED. Moreover, there is no nationally mandated public reporting program for emergency care. Hence, patients lack reliable guidance on ED provider performance. Due to these factors, current reporting efforts offer limited potential to improve substantially the quality of ED care for cancer patients. Five limitations of ED quality measurement in the USA are briefly discussed below: (1) gaps in existing ED measures; (2) fragmented measure development; (3) difficulty defining an episode of oncologic emergency care; (4) measurement without a clear mechanism for improving ED care; and (5) challenges in obtaining ED quality data.

Gaps in Existing ED Measures

A robust ED measure set for cancer patients should evaluate multiple dimensions of oncologic emergency care, including access, care coordination, advance care planning, patient and family engagement, and evaluation and management of acute and chronic conditions, as well as psychosocial needs. Routine measurement of outcomes, costs of care, and appropriate resource utilization is also essential. Yet, no existing measure set or quality reporting program adequately measures these aspects of oncologic emergency care. As noted above, 31 ED quality measures are endorsed or approved for trial use by the NQF as of July 2020. Eighteen of these measures are relevant to cancer care, including one cancer-specific measure. Current ED measurement gaps relevant to cancer care span measure categories—process, outcomes, cost/resource use, efficiency, and patients' perception-of-care—and include cancer-specific ED measures. These measurement gaps, together with recommendations to address these gaps, are summarized in Table 4.2.

Fragmented Measure Development

Historically, ED measure development efforts in the USA were academic-led and focused on specific patient populations or clinical conditions. These initiatives were conducted independently of payers and state and federal agencies, leading to a "patchwork of measures" for ED care [208]. These independent measure development efforts have contributed to the fragmented ED quality measurement observed today, which undermines efforts to deliver high-quality, patient-centered care. With few exceptions, existing ED measures have not been widely adopted by providers or payers. Thus, most ED care is not routinely measured, and existing quality measures provide an incomplete view of the nation's ED system. A well-coordinated approach to developing ED quality of care measures for oncologic is discussed later in this chapter.

Difficulty Defining an Episode of Oncologic Emergency Care

Defining an episode of emergency care is challenging for most conditions due to variations in the expected prognosis, treatment time, time to recovery, care teams, and treatment settings. Defining standardized episodes of oncologic emergency care is especially problematic for two reasons. First, cancer patients move frequently and unpredictably between care settings throughout the continuum of care. Therefore, cancer patients may present to the ED before diagnosis (for late-stage cancers presenting to the ED), at any point during treatment, and at the end of life. Second, the sequelae of cancer and its treatment vary greatly across patients. Therefore, cancer patients can present to the ED with symptoms of varying severity, ranging from moderate dehydration to life-threatening sepsis, making it difficult to standardize oncologic emergency treatment pathways across patients. Because episodes of oncologic emergency care can vary so greatly across patients, it is equally difficult to develop quality measures and appropriate benchmarks for care. Focused health service research is needed to develop episodes of oncologic emergency care with well-defined endpoints to support the development of relevant quality measures for this setting.

Measurement Without a Clear Mechanism for Improving Care

Quality measures designed for performance improvement and accountability should align with evidence-based guidelines, should be actionable by clinicians, and have a clearly defined relationship with patient outcomes. Moreover, measures should be reported publicly to inform healthcare consumers and to drive improvements in care. Public reporting of ED performance data has been proposed as a critical lever for improving the nation's emergency care system [35]. Ideally, existing quality measurement programs could be leveraged to measure the quality of emergency care across providers and care settings. However, the current programs are too narrowly focused to support a broad, system-level approach to measuring the quality of emergency care. Additionally, experience with publicly reported ED measures has produced mixed results. Some public reporting initiatives (e.g., AMI performance measures) have generated significant improvements in care,

while others (e.g., pneumonia performance measures) have yielded disappointing results or—even worse—poorer quality of care. In those cases, the measures were misaligned with the existing guidelines, were based on weak evidence, or included arbitrary time points [208]. Additionally, flawed attribution models may generate erroneous conclusions regarding the quality of ED care and impede efforts to address quality of care issues. These limitations must be addressed to ensure that ED quality measures can support meaningful improvements in care, particularly for oncologic where multiple providers and care settings share responsibility for their outcomes of care.

Challenges in Obtaining ED Quality of Care Data

Much has been published in recent years regarding the limitations of existing data to support robust, actionable quality measurement. Historical quality measurement leveraged administrative claims data, which are relatively easy to access but are not designed for quality reporting. At best, they offer an incomplete view of healthcare quality. At worst, the data may be irrelevant, incomplete, or inaccurate. Federal agencies and EHR vendors have promoted EHRs as a viable alternative to address these data issues. However, EHRs were designed to support healthcare operations, rather than quality measurement, and early assessments of EHR-based quality reporting have been disappointing [221–223]. Manual chart review and data entry remains a primary method of collecting data—or supplementing electronic data—to produce quality measures. The level of effort and reporting lag associated with this approach limit access to the data that are critical for timely, actionable, and meaningful ED quality measurement. Moreover, because ED physicians often lack an established and ongoing relationship with their patients, they often lack access to immediate and long-term data on the outcomes of ED care. Potential strategies to address these issues are described later in this chapter.

Desired State of National Quality Measurement for Oncologic Emergency Care

In reviewing the history and current state of national quality measurement for emergency medicine, several important themes emerge:

1. There is widespread acknowledgment of the essential role that EDs serve in the nation's public health system.
2. Quality issues in emergency medicine are well documented, and healthcare experts have developed practical recommendations to address many of these issues.
3. Some quality issues observed in the ED are unrelated to the quality of emergency care and, instead, reflect broader social issues (e.g., inadequate access to healthcare) or quality of care issues in other healthcare settings.
4. Public and private organizations have recognized that quality measurement is integral to ED quality improvement, and early successes in cardiovascular emergency medicine have demonstrated how ED-based national quality measurement can be leveraged to improve patient outcomes.
5. HIT advancements, together with increased adoption of EHRs, offer the potential to give ED providers greater access to the data needed to care for their patients and to evaluate their quality of care on a more real-time basis.

While not specific to oncologic emergency care, these accomplishments represent a solid platform to address existing measurement gaps through national reporting for oncologic emergency care. There are five factors that contribute to the current state of inertia we described earlier in this chapter: (1) gaps in existing ED measures; (2) fragmented measure development; (3) difficulty defining the episode of oncologic emergency care; (4) measurement without a clear mechanism for improving ED care; and (5) challenges in obtaining ED quality data. Many of these factors stem from substantial shortcomings in the funding, oversight, and coordination of measure development and public reporting for cancer care.

In this section, we outline a vision for measuring quality in oncologic emergency care, through the implementation of the NAM's recommendation to create a comprehensive national quality reporting program for cancer care. This includes a well-coordinated approach to developing cancer-specific ED quality of care measures. We also propose healthcare policy changes that will promote better alignment between public reporting and reimbursement for oncologic emergency care and that will promote shared accountability across providers. Additionally, we describe how the NAM's recommendation to implement a learning healthcare system for cancer could address many of the challenges in obtaining ED quality of care data. Finally, we share a sample case study describing how ED and palliative providers can partner with palliative care providers to address upstream gaps in care to reduce ED visits.

Vision for National Quality Measurement in Oncologic Emergency Care

Since 1999, the NAM has promoted national quality measurement as an essential lever to improve the quality of US cancer care delivery. In 2013, the NAM released *Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis*, which outlined six compo-

nents of a high-quality cancer care delivery system: (1) engaged patients; (2) an adequately staffed, trained, and coordinated workforce; (3) evidence-based cancer care; (4) a learning healthcare information technology system; (5) translation of evidence into clinical practice, quality measurement, and performance improvement; and (6) accessible, affordable cancer care [84]. The report identified the nation's inability to systematically measure and improve cancer care delivery as a primary contributor to existing gaps in cancer quality and offered the following recommendation:

Recommendation 8: Quality Measurement

Goal: Develop a national quality reporting program for cancer care as part of a learning healthcare system.

To accomplish this, the Department of Health and Human Services should work with professional societies to:

- Create and implement a formal long-term strategy for publicly reporting quality measures for cancer care that leverages existing efforts
- Prioritize, fund, and direct the development of meaningful quality measures for cancer care with a focus on outcome measures and with performance targets for use in publicly reporting the performance of institutions, practices, and individual clinicians
- Implement a coordinated, transparent reporting infrastructure that meets the needs of all stakeholders, including patients, and is integrated into a learning healthcare system [84]

Implementation of this national quality reporting program for cancer care would enhance quality measurement within the ED and across other care delivery settings. It would support purposeful, well-coordinated, and patient-centered quality measurement in the ED, with an emphasis on care coordination and shared accountability across providers and care delivery settings. Through public reporting, it would encourage evidence-based care delivery and patient engagement while discouraging unnecessary—*and potentially harmful*—care. By increasing transparency around the outcomes, processes, and costs of cancer care, the national reporting program envisioned in the report could expedite progress toward a high-quality cancer care delivery system, of which the ED is an essential component. Adequate funding, formal leadership, strong collaboration, and HIT enhancements, together with a well-developed framework and a unified strategy, are essential to its successful implementation, as discussed below.

Health Policy for Measuring Quality in Oncologic Emergency Care

As described earlier in this chapter, EMTALA and the no-duty-to-treat principle form the health policy base for emergency care in the USA. While EMTALA facilitates patient access to emergency medical care, it does not regulate the quality of that care. More recently, the MMA, DRA, Tax Relief and Health Care Act of 2006, and MACRA introduced and reformed national quality reporting for emergency care. The quality reporting stimulated by this legislation has done little to promote high-quality oncologic emergency care because it focused largely on other conditions, such as cardiovascular disease.

To advance quality in the nation's oncologic emergency care, national quality reporting for cancer care is essential, as recommended by the NAM. The frequency, complexity, and costs of oncologic emergency care, particularly at the end of life, necessitate a well-coordinated and unified approach to address current measurement gaps in oncologic emergency care. Thus, we offer the following policy recommendations in support of this effort:

- *Leadership and Collaboration*: *Delivering High-Quality Cancer Care—Charting a New Course for a System in Crisis* identified HHS as the appropriate organizer of this work. Through collaboration with patient advocacy organizations, professional societies, payers, and other stakeholders, HHS could ignite national development of quality measures for oncologic emergency care. Designating CMS and the NQF as key partners in this effort could accelerate progress in developing validated cancer-specific ED quality of care measures.
- *Formal Long-Term Strategy*: Create and enforce a formal long-term strategy (with shorter-term milestones) and a well-defined framework for the development and public reporting of measures for oncologic emergency care (as part of a broader strategy and framework for cancer). This long-term strategy would address the needs of all cancer patients, with a particular focus on cancer patients seeking emergency care at the end of life. Moreover, by moving away from quality measurement focused on specific Medicare payment programs, it would promote shared accountability by providers.
- *Research*: Fund health services research and clinical trials to expand the scientific evidence for oncologic emergency care, including:
  - Effective care coordination between outpatient oncologic and ED providers
  - Outpatient care delivery models that reduce unnecessary ED utilization among cancer patients

  - Approaches to mitigate the overutilization of ED services by cancer patients, particularly at the end of life
  - Episodes of oncologic emergency care, with well-defined endpoints and treatment pathways
  - Strategies to address the psychosocial needs of cancer patients with advanced disease and their caregivers
  - Drivers of late-stage cancers presenting to the ED
  - Care delivery models that integrate palliative care with ED services
- *Measure Development*: Fund the development of a robust set of meaningful measures for oncologic emergency care (including performance targets) for use in public reporting. Measure development should focus on the outcomes of care as well as access to care, care coordination, advance care planning, patient and family engagement, and evaluation and management of acute and chronic conditions, as well as psychosocial needs. High-priority measurement gaps are described in Table 4.2. Prioritization of measure development should align with the formal long-term strategy guiding this effort and target likely healthcare disparities. Moreover, measure development should have a well-defined cost-benefit relationship and should foster shared accountability across providers and including patients. Where appropriate, the developed measures should address multiple care delivery settings. Measures available from existing data sources should receive higher priority. However, lack of data should not constitute a barrier to measure development. A formal tool should be developed to assist the collaborative in prioritizing measure development [224].
- *Transparent Reporting Infrastructure*: As recommended by the NAM, implement a reporting infrastructure (including IT infrastructure and reporting methodologies) that promotes transparency of the outcomes that are most meaningful to patients and their caregivers and that meets the information needs of all stakeholders (patients and their caregivers, providers, payers, and state and federal agencies). Public reporting should be understandable by patients and their caregivers to support healthcare decision-making.

Expedited adoption of health policy in support of these priorities would do much to address the existing measurement gaps for oncologic emergency care. With multistakeholder collaboration among organizations that share a vested interest in oncologic emergency medicine as well as proper funding and authority, robust national quality measurement for oncologic emergency care could become a reality within a few years.

HIT Support Through the Learning Healthcare System for Cancer

Providers face significant obstacles in obtaining timely, actionable, and comprehensive data to support the robust quality measurement described herein. Additionally, because ED providers lack an established and ongoing relationship with their patients, they often do not have access to post-discharge and longitudinal outcomes data to support meaningful quality measurement. To advance meaningful quality measurement and public reporting, *Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis* advocated the creation of a learning healthcare system for cancer [84]. A learning healthcare system streamlines provider data collection and reporting and enables real-time data analysis for performance improvement, quality measurement, and clinical decision support. The cancer-specific learning healthcare system described by the NAM would support more rapid innovation in cancer care delivery by addressing critical data gaps in two ways: (1) by capturing provider-driven clinical data, patient-reported outcomes, and patient and caregiver experience with care in a structured format and (2) by integrating structured, unstructured, and semi-structured data. National endorsement of this recommendation would address many of the data gaps described in this report and would enable development and reporting of quality measures for oncologic emergency care. To be successful, federal incentives to promote HIT adoption (e.g., Meaningful Use) should incorporate the principles of a learning healthcare system for cancer [225]. Likewise, public and private payers should reward providers for participating in a learning healthcare system for cancer. Aligning provider incentives with adoption of a learning healthcare system for cancer would enhance the current IT infrastructure and promote widespread access to the information needed to catalyze national public reporting for oncologic emergency care.

Role of Targeted Quality Measures in Driving Practice Change

As noted earlier in this chapter, quality measures provide a standardized, objective means of evaluating healthcare quality and hold an important role in the US healthcare delivery system. State and federal agencies utilize quality measures to promote provider accountability and to inform the public. Increasingly, payers are using quality measures in value-based payment programs to align reimbursement with quality of care. Because cancer patients experience unique

quality of care issues and because most disease-specific ED measures focus on non-cancer conditions, the existing ED quality of care measures offer minimal opportunity to improve the quality of oncologic emergency care. Despite these limitations, *appropriately selected* quality measures have the potential to inform consumer decision-making and care planning, accelerate improvements in care, and highlight variation between providers and over time within a given practice setting [84]. Additionally, routine quality measurement and reporting enables payers and providers to test whether new care delivery and payment models have a positive effect on the accessibility, quality, and affordability of healthcare.

Public reporting of well-designed quality measures for oncologic emergency care represents a powerful policy lever to encourage more appropriate ED resource utilization, better care coordination, shared accountability, and, ultimately, superior outcomes and patient (and caregiver) experience with care. Lamb et al. observed that the act of measuring performance at the provider level can ignite an interest in self-improvement or a competitive spirit among providers, leading to improvements in care [226]. Pay-for-performance programs are another policy lever that could lead to improvements in the quality of oncologic emergency care. The effectiveness of pay-for-performance programs has been debated extensively, given current measurement gaps across multiple conditions and various aspects of care. However, designing a pay-for-performance program around targeted quality measures for oncologic emergency care (such as those listed as measure development priorities in Table 4.2) could stimulate significant and lasting improvements in care.

Conclusion

In this chapter, we examined the history, current state, and desired future state of health policy for quality in oncologic emergency care. We discussed five quality issues that cancer patients experience when seeking care in the ED, together with upstream drivers. We also described specific issues for dedicated oncologic EDs. We highlighted the essential role of quality measures in addressing these quality of care issues, along with five limitations of the existing quality measures that apply to emergency care. We also shared the quality measures for emergency care that are currently endorsed by the NQF and used in CMS quality reporting programs. We outlined recommendations for national quality measurement for oncologic emergency care, through the implementation of the NAM's recommendation to create national quality reporting for cancer care, as part of a learning healthcare system. We proposed health policy changes—in the form of leadership and collaboration, formal long-term strategy, research, measure development, and transparent reporting infrastructure—to accelerate progress toward national quality measurement for oncologic emergency care. We emphasized the importance of adequate funding, formal leadership, strong collaboration, and HIT enhancements to make this reporting a reality. We also explained how a learning healthcare system for cancer and targeted quality measures can catalyze change and advance progress toward the national reporting program described herein. Additionally, we shared a sample case study outlining a collaborative approach to address unmet palliative care needs in the ED.

The recommendations outlined in this chapter are ambitious but are necessary to accelerate the development of targeted quality measures for oncologic emergency medicine. To be successful, measure developers and other stakeholders must abandon the historical practice of siloed development of highly specific measures that apply to a small proportion of the population or to a single care delivery setting. With adequate funding, unified leadership, and multi-stakeholder commitment, national quality reporting for oncologic emergency medicine could become a reality within a few years, leading to more patient-centered and higher-quality cancer care in the ED.

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Patient Navigation

5

David C. Seaberg and Donald Norris II

Introduction

Cancer patients face significant challenges. This is true not only with their illness but also when trying to navigate an increasingly matrix-oriented healthcare system. While advances in cancer treatment have helped save millions of lives over the last three decades, patients face far more complex treatment decisions and follow-up options than ever before. The amount of time required and the types of services cancer patients utilize have expanded across the spectrum of prevention, screening, diagnosis, treatment, and survivorship. As more cancer patients live with chronic illness, the length of time a patient is engaged with the healthcare system, including the emergency department (ED), has increased. Efforts made by healthcare systems to enhance patient experience and coordinate care have become increasingly more important.

Patient navigation is seen as one possible solution to this problem. Patient navigation has been shown to improve timely cancer care [1–4]. Patient navigation programs reduce gaps in care by improving access to cancer services, improving the timeliness of the provision of these services, and adding strong support and guidance to patients [5]. Patient navigation involves collaboration between patients, providers, families, and caregivers. Their collaboration extends throughout the cancer continuum, from prevention and screening through treatment, survivorship, and palliative and end-of-life care. These programs employ a variety of individuals from laypeople to trained nurses and social workers to assist patients.

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US emergency departments are an increasingly important site of care for patients with complex care needs. Specifically, ED visits for patients with cancer now exceed 4.5 million annually [6, 7]. ED visits for individuals aged 65 years and older now number nearly 30 million [8]. Many of these patients lack essential health knowledge including an understanding of the resources they need to optimize their health. Patient navigator systems help patients with complex care needs navigate the multifaceted and fragmented medical systems.

Case Study

Charlotte, North Carolina-based Atrium Health's Levine Cancer Institute developed a patient navigation program that featured 25 nurse navigators spread across seven locations. Patients who did not receive navigation services were 52% more likely to have unplanned hospital readmissions within 30 days when compared with patients who did. In a retrospective cohort study of approximately 2300 patients with poor prognosis (as defined by the American College of Surgeons [ACS]), the program found a significant survival benefit for patients who had received navigation services compared with those who had not. The greatest survival advantage was seen in patients who were either African American, were insured by Medicaid, or had lung or pancreatic cancer [9].

Background

Patient navigation is an intervention to reduce health disparities in cancer care. It is specifically aimed at vulnerable or medically underserved populations. The first patient navigator program was created by Harold Freeman in 1990 at Harlem Hospital in New York, NY. He focused on underserved women with breast cancer [10, 11]. The goals of the program were to expand access to cancer screening, improve

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clinical follow-up among medically underserved women through community outreach, and reduce the time between an abnormal test result and diagnosis and/or treatment [12]. Eliminating barriers to health access, such as lack of insurance or cultural and communication barriers, was also critically important. The navigation program was remarkably successful with an increased 5-year survival of 31% [10, 11].

In the 30 years since Dr. Freeman's initial program, the use of patient navigator programs has spread to other cancer treatment programs as a means to decrease barriers to care and improve overall outcomes for disparate populations. Many of the current patient navigator programs were initially focused on providing guidance to the racial/ethnic minority or low-income populations. In 2001, the President's Cancer Panel was established with the National Cancer Act of 1971. It revealed that barriers limiting or preventing access to cancer care are not unique to poor Americans but were experienced by Americans across all socioeconomic levels [13, 14]. The panel found multiple reasons why people of all socioeconomic levels were not getting screened and treated. These were primarily related to fear, literacy, culture, and religion [15, 16]. In 2005, the Outreach and Chronic Disease Prevention Act was signed, providing financial grants for the development and operation of patient navigator services to improve healthcare outcomes across the entire country. Each approved hospital was to add a full-time navigator program [17]. In 2012, the ACS Commission on Cancer released standards that reflected the goal of "ensuring patient-centered care." One of the new standards (Standard 3.1) required all cancer programs seeking accreditation to have a patient navigation program [18, 19].

As the importance of patient navigation has been recognized, the role of nurse or patient navigators and the terms used to describe these individuals and their functions within the oncologic care team have evolved.

The National Cancer Institute (NCI) describes patient navigation as the support and guidance provided to persons with abnormal screenings or new cancer diagnoses, including overcoming challenges and barriers to accessing the healthcare system in a culturally competent manner [20–23]. They state that the role of a navigator is to help patients and their families assess the cancer care system and overcome barriers to receiving care. This includes facilitating the provision of timely, quality care in a culturally sensitive manner [15, 24]. Specific time points in the cancer continuum are the focus, and the goal is to reduce the complexity of the healthcare system for the patient [25].

Management

Patient navigation is provided to individual patients for a defined episode of cancer-related care. The goal of patient navigation is to provide an intervention that addresses barriers to quality standard care by providing individualized assistance to patients, survivors, and families [9, 26, 27]. Reducing time to access healthcare resources is critical for the patient. Oncologic navigators bridge the gap between health systems and the patient. An obvious byproduct of a successful cancer navigation program is decreased visits to the ED for these patients [28]. Navigators have the ability to effectively communicate with providers and other stakeholders within and across the institution while serving patients as knowledgeable, caring peers, and allies who have an inside track to the health system [29]. Patient navigators help patients address barriers ranging from communication to psychological or financial needs and health systems social support-related issues. Other common topics in oncologic navigation are [30]:

- Financial and economic issues
- Differences in language, which may prevent patients and family from understanding treatment recommendations
- Cultural and ethnic diversity requiring tailored interventions
- Communication among healthcare teams, patients, families, and other healthcare providers
- Transportation problems that impact patients' ability to receive healthcare
- Emotional concerns for patients including distress and fear, which may prolong decision-making and delay interventions

Oncologic patient navigators perform many roles. The navigators help reduce barriers to healthcare services through educating patients on their diagnosis/treatment and build partnerships in the community. Additionally, they help coordinate appointments, maintain communication, connect patients and families with support services, teach self-advocacy, and provide access to clinical trials. There are multiple roles in patient navigation yet no universally accepted definition. There is no consensus on necessary preparation and competencies for filling the role [31–33].

Oncologic Nurse Navigator

An oncologic nurse navigator (ONN) is a professional registered nurse with oncologic-specific clinical knowledge who offers individualized assistance to patients, families, and caregivers to help overcome healthcare system barriers and facilitate informed decisions [31, 32]. They ensure that the patient receives timely access to quality health and psychosocial care throughout all phases of the cancer continuum. In 2009, the National Coalition of Oncologic Nurse Navigators (NCONN) developed the first competencies that defined the role of the ONN [34–36]. Developed in consultation with

active professional oncologic nurse navigators throughout the United States, these core competencies cover five areas: (1) professional, legal, and ethical nursing practice; (2) health promotion and health education; (3) management and leadership; (4) negotiating the healthcare delivery system and advocacy; and (5) personal effectiveness and professional development [36, 37]. The first published guidelines establishing core competencies for ONNs were established by the Oncologic Nursing Society in 2013 [37, 38].

Oncologic Social Worker

Oncologic social workers are knowledgeable about cancer and the psychosocial and other effects of disease, treatment, and survivorship. They have advanced degrees and have additional experience and training in oncologic and other life-threatening illnesses. The oncologic social work navigator helps foster coping and adaption to cancer and its effects in order to help cancer survivors maintain or improve quality of life [38]. Their focus in clinical practice is to help complete a psychosocial assessment to determine survivor and family strengths and needs relative to coping effectively with cancer diagnosis, treatment, and follow-up care [39]. They work with other team members to develop a multidisciplinary care plan and help provide case management services. They also provide direct assistance to help meet financial, transportation, lodging, and other psychosocial needs, including end-of-life advance care planning [39]. Oncologic social workers also assist survivors in navigating through healthcare systems to help them achieve quality care. They help provide social and emotional support to cancer survivors by mobilizing new or existing family, system, and community resources [30]. In addition, oncologic social work navigators advocate with, or on behalf of, survivors, families, and caregivers to address their needs as well as advocate for policies and programs that will benefit them.

Lay Navigator

A lay navigator is a trained nonprofessional or volunteer who provides individualized assistance to patients, families, and caregivers [40]. They help overcome healthcare system barriers and facilitate timely access to quality healthcare and psychosocial care, from pre-diagnosis through all phases of cancer care. Interestingly, Dr. Freeman's original patient navigation program believed that the role of the navigator should be served by a layperson and not by a nurse or social worker [41].

Navigators can be disease, condition, or service specific, with many specializing in areas such as breast, prostate, or lung cancer. Some navigators focus primarily on the role of financial navigator. Others may provide assistance in the areas of screening and testing, as the original navigators did. Patient navigation in cancer care currently focuses on assisting patients in the coordination of care among providers, the community, and patients and their families [12, 42–44]. To move patient navigation forward, the cancer community will need to develop and agree upon a streamlined definition that can be promoted by all stakeholders and understood by patients and their families [45].

Patient-Centered Medical Home

The concept of a patient-centered medical home (PCMH) originated in pediatric literature dating to the late 1960s. Originally conceived as a way to integrate care for children with special needs, physicians soon realized that fragmented care was seen in the general pediatrics population as well. In 2007, the American College of Physicians, American Academy of Family Physicians, American Osteopathic Association, and American Academy of Pediatrics drafted the Joint Principles of the Patient-Centered Medical Home. This document defined the PCMH placing the relationship between the patient and their primary care physician at the center. While the primary physician maintains a longitudinal relationship with the patient, they also lead the team of other individuals integral to the overall care of the patient. Emphasis was placed on quality and safety leading to an overall reduction in cost with higher quality of care [46].

An additional positive outcome often mentioned when discussing the PCMH is a reduction in visits to the emergency department. The American College of Emergency Physicians (ACEP) released a policy on patient-centered medical homes in 2008 revising the policy in 2015. In this policy, ACEP fully supports the PCMH if it upholds the following principles:

1. Provide high-quality, safe, and efficient medical care
2. Provide patient access to a personal physician, the leader of a team of individuals who collectively take responsibility for ongoing care of their patients
3. Ensure patients have the freedom to select a specialist of their choosing and access emergency medical care when they feel they need it
4. Include the safety net of emergency care [47]

In 2012, the Michigan Oncologic Medical Home Demonstration Project was developed. It was one of the first multi-practice oncologic medical home projects in the country. Placing the oncologist and patient at the center of the design, this group standardized development of treatment regimens including deployment of enhanced triage and access protocols. The group also standardized advance care

planning across the groups. In addition, a medical home nurse line was established to help triage patients seeking unscheduled care. In the first year of the 85-patient pilot program, the overall cost savings was $550 per patient [48].

Health Services/Resource Utilization

Patient navigation programs and the backgrounds of those who serve as patient navigators are driven by local needs. There is no one type of patient navigation model that fits the needs of all medical settings or systems. Healthcare organizations that start patient navigation programs need to assess the needs of their populations and tailor the intervention to those needs. Patient navigation is typically a goal-oriented intervention that focuses on reducing the barriers to achieving a particular cancer healthcare goal, such as improvements in cancer screening rates, cancer treatment adherence, or patient satisfaction with care [12, 23]. Particular emphasis on implementing patient navigation interventions should focus on improvements in a particular outcome of interest. Although individual patients may benefit from actions taken by patient navigators across the cancer care continuum, current literature shows that interventions that target cancer screening outcomes have the greatest clinical benefit and most cost-effectiveness [49].

Patient navigation programs have had many successes. The Patient Navigation Research Program (PNRP) was designed to develop interventions to reduce the time to diagnosis and treatment of cancer after identifying an abnormal finding from a cancer detection procedure. The PNRP studies, enrolling over 10,000 patients, found that patient navigation reduced the time from abnormal findings to diagnosis in breast, cervical, colorectal, and prostate cancers [50]. Resolutions of cancer therapy at 180 days and at 270 days with navigation were 56.2% and 70.0%, respectively, compared with 53.8% and 68.2%, respectively, with usual care. The estimated cost of navigation in this study was $275 per patient.

Patient navigation services have proven to be effective at reducing the cost and improving the quality of care for patients with cancer. Patient navigation has been found in survey studies to increase patient and staff satisfaction while decreasing barriers to care. One study published by The Ralph Lauren Center for Cancer Care and Prevention in New York found improved cost-effectiveness for patients with breast and colorectal cancer [51]. Researchers found that patient navigation led to patients achieving diagnostic resolution with shorter treatment intervals. There were significant cost savings per patient at the end of treatment. A study at the George Washington Cancer Institute in Washington, D.C., found that the patient navigation program significantly reduced breast cancer diagnostic time. Use of patient navigation in the emergency department was found to decrease overall patient and hospital costs as well as reduce subsequent emergency department visits [4].

Adding care coordination to patient navigation has proven to have many benefits to physicians, patients, and their families. It enhances interaction among physicians, increases patient awareness and self-management, and improves patient education and satisfaction [52]. It also increases referrals for nutrition and physiological care as well as physical and social service needs [52, 53]. For the patient and the family, care coordination simplifies the process. Care coordination also facilitates access to ancillary and community services and resources. Other benefits include improved education of patient and family, increased collaboration and communication among the patient and the healthcare team, improved patient self-care and satisfaction, and increased multidisciplinary care [23].

ED visits have increased exponentially over the last three decades now topping 140 million per year [8]. Long recognized as a safety net provider, the ED is a usual source of care for those who are affected by barriers to continuity relationships with physicians as well as patients with complex medical problems requiring a coordinated care approach. Initial evidence suggests that patient navigators may help remove barriers to timely, effective patient care among vulnerable populations which may, in turn, influence ED utilization [54, 55]. In a survey of oncologic patient navigators, 91% indicated that lay navigation services would be either very helpful or moderately helpful for ED patients with cancer. Coordination of care, the provision of emotional support and educational resources, and providing companionship to older persons during the ED visits were identified as priorities for an ED-based lay navigation program. The three most common barriers that emergency department patient navigators help patients with include insurance and out-of-pocket expenses, transportation issues, and helping manage the feelings and fears associated with cancer [56]. Follow-up appointments and getting prescriptions filled were also important considerations. Funding for ED navigation programs came initially through small foundational grants for pilot programs. As the value and role of navigation programs have become more defined, hospitals have increasingly funded ED navigators who consist of teams of transitional care coordinators, case managers, and lay personnel.

There have been numerous emergency department studies on the use of patient navigation in patients who utilize the ED frequently. It has been reported that just 5% of ED patients comprise nearly 25% of all ED visits yearly [57, 58]. Though the reasons for this are multifactorial including low-income status, lack of insurance, severe chronic illnesses, and lack of primary care provider and familiarity, the cost to the patient and the community is exceedingly high [59, 60]. The cost to both the patient and community is not just monetary; care of these patients is inappropriately fragmented.

ED patients who frequently utilize the ED contribute to overcrowding affecting the community's emergency readiness. In one study, paid social work staff were trained to help patients navigate their healthcare options during their ED visit by educating the patient on their diagnosis, reviewing the associated treatment and follow-up plans including medications, and identifying proper primary care services and/or community resources that can aid with the patient's specific issues [58]. This study found that a patient navigator program reduced 1-year ED visits and costs by 9%. It was found that the majority of high utilizers had primary care providers as well as insurance. Lack of health literacy impacts their ability to navigate the health system. Lack of communication, lack of preventative care, referral options, and a cultural distrust led to poor outcomes and overutilization of the ED. Patient navigation has been shown to improve health outcomes and reduce costs [61, 62].

Another study by the Highmark Foundation found that patient navigators in three health systems were able to reduce excessive emergency department visits by 43% over 1 year [28]. In addition to the decrease in emergency department visits, one health system reported a 60% reduction in 30-day readmission, and another reported increased colonoscopy screening by 13%. The certified patient navigators in the study were laypersons who helped with nonclinical tasks such as picking up prescriptions, arranging transportation, connecting patients to community resources, and conducting post-discharge follow-ups [28].

A study at the Memorial Hermann Health System in Houston developed a patient navigation program designed to promote appropriate primary and oncologic care utilization and prevent or reduce ED use [63]. The navigators consisted of bilingual, state-certified community health workers who were trained in peer-to-peer counseling and connected medically underserved patients with medical homes and related support services. The navigators provided education about the importance of follow-up care, assisted with appointment scheduling, and followed up with patients to monitor and address additional care barriers. Over a 12-month period, ED visits declined as did medical costs [63].

Future Needs/Vision

Patient navigation needs to define the roles within the patient navigation team. Research has shown that there are similarities between the improvements in outcomes associated with patient navigation and those associated with care coordination [24]. One study reported that coordination and continuity of care were similarly important to the roles of patient navigator, nurse care manager or coordinator, and nurse navigator, for improving outcomes [33]. Another report suggested that professionally led models of patient navigation that were similar to comprehensive case management models—adding the supportive functions of advocacy, education, problem solving, and support to the standard model of assessment, outreach, and referrals—were favorable to other models [33, 64]. Coordination of care and ensuring continuity of care were described as overarching roles and responsibilities in an integrative review [64]. The future of patient navigation revolves around integrating the navigation team within the patient-centered medical home. Defining the roles within the navigation team will be essential to achieving specific clinical outcomes as well as creating efficiency and cost-effectiveness. In order to achieve their effectiveness, patient navigation programs will need to expand more to outpatient areas including the emergency department.

The new standard set by the ACS CoC in establishing patient navigation programs in all ACS CoC-accredited facilities has led to enhanced funding for navigation programs [64]. Further work is needed to demonstrate the value of the blended model patient navigation care coordination. Further studies will be needed to evaluate the economic impact of the patient navigation programs. Cost-effectiveness analysis and budget impact studies are needed to further refine these patient navigation programs in the patient-centered medical home. The Health Services Research (HSR) cost workgroup of the American Cancer Society National Patient Navigator Leadership Summit met to examine cost data relevant to assessing the economic impact of patient navigation and to propose common cost metrics. Five categories of core and optional cost measures were identified: program costs, human capital costs, direct medical costs, direct nonmedical costs, and indirect costs [64]. The researchers recommended adoption of these metrics to promote understanding of the economic impact of patient navigation and comparability across diverse patient navigation programs. Further funding opportunities will need to be explored to enhance the development of these patient navigator programs.

Conclusion

Models of patient navigation and care coordination must continue to evolve to meet the ever-changing needs of cancer patients and their families. New models must hold fast to the guiding principles of the original navigation program: improve access to the cancer care system and facilitate quality care. These programs will not only lead to more rapid diagnoses, improved patient outcomes, and increased cost savings, but they will also ensure greater patient adherence to treatment programs. With the increasing use of clinical pathways in oncologic, and the need to demonstrate the value of these pathways, navigation and care coordination programs can be effective tools for maximizing the quality of

care provided to patients. Expansion into the outpatient setting and emergency department may further increase the effectiveness and lead to both improved clinical outcomes and cost savings.

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Nursing

6

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Emergency Nursing and Oncologic Emergencies

In 2011, the American Nurses Association recognized emergency nursing as a specialty practice. As a challenging and unique profession, this clinical practice area prepares nurses to provide prompt interventions to stabilize or prevent further patient deterioration. The fast-paced, high-acuity setting commands refined critical thinking, clinical assessment, communication, and prioritization skills. Additionally, emergency nurses (ENs) care for a diverse patient population with various medical conditions and acute care needs [1].

Of significance is the Emergency Nursing Association (ENA), founded in 1970 as the premier professional nursing association, devoted to illustrating the future of emergency nursing. The mission of ENA is to further excellence in emergency nursing [2].

Reflective of the diverse nature of healthcare, emergency medicine has multiple subspecialties. As such, different emergency departments (EDs) provide care to specific patient populations and health concerns. Some of the subtypes include trauma, stroke, cardiac, burn, neuro, disaster response, pediatric, and adult [3].

The same variations that exist in emergency medicine and EDs are also depicted among ENs. It is not surprising to find that most ENs assume multiple roles over the course of their career. Some of these roles include *trauma, triage, flight, critical care transport, pediatric, burn center, geriatric, and charge nurse* [3].

Professional advancement has also led to further specialization of ENs. This year, the Board of Certified Emergency Nursing recognized four different subspecialty professional certifications, including the *Certified Emergency Nurse*, *Certified Flight RN, Certified Pediatric Emergency Nurse, Certified Transport Registered Nurse, and Trauma Certified Registered Nurse* [3]. Notably, as professional advancement continues to detect emerging areas of subspecialty in emergency nursing, additional professional certifications, education, and targeted programs have been created to support quality care [3].

One emerging subspecialty is Oncologic Emergency Nursing (OEN), a clinical practice designed to provide care for patients presenting with cancer emergencies.

Consider this: the 5-year survival rate for all cancers increased from 39% in 1960 to nearly 70% in 2019 and thanks in part to new cancer treatment modalities, increased survival rates have led to approximately 15 million people in the United States with cancer. The majority of these individuals likely experience oncologic emergencies requiring an ED visit [4]. OEN is among the healthcare teams that assume multiple roles in the ED to provide quality care and ensure optimum health outcomes for the patients presenting with oncologic emergencies.

This chapter identifies high-frequency and high-risk conditions that an OEN may encounter when caring for an ED oncologic patient. For each condition, we then present a number of case studies to illustrate several medical diagnoses, associated risk factors, presenting signs and symptoms, potential causes, contributing factors, anticipated diagnostics, corresponding interventions, case dispositions, and specialty nursing considerations. We conclude with discussions of the impact of the pandemic (novel coronavirus) on cancer patients and an overview of regulatory bodies that guide ED practice in the oncologic setting.

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Triage and General Assessment of Oncologic Emergencies

Triage

At triage, patients presenting to ED will encounter the triage nurse as the first medical professional. The role of the triage nurse is to identify patients needing immediate attention and then prioritize among those who do not require immediate life-saving interventions. Triage tools, such as the Emergency Severity Index (ESI), are used to standardize the approach and to predict patient disposition and ED resource use [5]. The ESI is a reliable and valid tool that is now in its fourth version [5], and is the most commonly used ED triage system in the United States [6]. The tool provides clinically relevant grading of patients into five groups from 1 (*most urgent*) to 5 (*least urgent*). This stratification is based on patients' acuity and resource needs [7].

Typically, patients with cancer have an ESI level of 1, 2, or 3 because of their potential to use multiple resources due to the complexity of their condition. Beyond the primary assessment is the need to screen for patients' cancer diagnoses, last treatment and modality, and any other significant surgeries or procedures [7].

General Assessment

ED nurses' ability to perform an accurate initial comprehensive patient assessment after triage is imperative in order to recognize the urgency and treatment needs of patients and to develop baseline data from which any changes in the condition of patients may be measured against [8].

Omission of accurate and timely patient assessments has been reported to result in adverse patient outcomes [9].

The EN can also expect the medical team to order laboratory tests. General labs should be assessed on almost all cancer patients, as treatment and disease processes may alter values from day to day and can likely provide additional insight into the underlying issue. Obtaining a complete blood count (CBC) with differential and comprehensive metabolic panel (CMP) is indicated for the vast majority of patients with a concurrent cancer diagnosis. Determining a patient's pancytopenia status, electrolyte levels and overall metabolic status are critical, as many abnormalities may not have associated symptoms in early stages. Early detection and correction of imbalances may prevent patients from incurring further injury or deterioration [10].

Although patients with cancer may present with an array of medical emergencies, this population is also at a high risk for infection. As such, sepsis should always be considered. Any signs or symptoms of infection should be promptly noted and addressed, as these patients are immunocompromised and have little physiological defense mechanisms. The presence of a central line also increases infection risk [11]. Timely collection of blood cultures and prompt administration of broad-spectrum antibiotics for any suspected infection can significantly improve the patient's prognosis [12].

Frequent ED encounters for patients with advanced cancer may also indicate a patient nearing end of life [13]. Patients with advanced cancer may benefit from conversations about advance care planning and code status to ensure their wishes are followed in the care trajectory. Although such conversations may be difficult, they can significantly improve the patient and family experience. Sending patients home with hospice from the ED is, at times, a feasible and appropriate option [14].

Chief Complaint: Chest Pain and Shortness of Breath

Patients presenting with chest pain and shortness of breath should be evaluated immediately for acute myocardial infarction via EKG. If EKG results do not suggest an acute MI, additional diagnostics should be employed to determine the underlying issue [15]. Chest pain and shortness of breath in cancer patients can be caused by various conditions that are common among cancer patients. These include pulmonary embolism, pleural effusion, pneumonia, spontaneous pneumothorax due to tumor burden, pericardial effusion, and cardiac tamponade [16]. See case studies in Table 6.1 illustrating a number of presentations involving these chief complaints [17–25]. Due to coagulopathies and bleeding tendencies, cancer patients may be at higher risk of cardiopulmonary-related adverse events [26]. As increasing numbers of patients receive immune checkpoint therapy, some cardiac presentation may represent immune-related adverse effects [27].

Tumors are known to cause collections of fluid proximal to tumor location. Depending on known lesions, tumors in the thoracic cavity may provide further insight into contributing conditions [28]. Pleural effusions are a high-frequency finding in lung cancer patients or patients with lung metastases. In recurrent pleural effusions, patients may have a Denver catheter drain placed to manage the fluid collection and reduce symptoms. If pleural effusion is identified, patients may require thoracentesis. This will likely alleviate any shortness of breath or chest pain symptoms almost immediately [29].

Table 6.1 Case studies: chest pain and shortness of breath

Vital signs	Signs and symptoms	Risk factors/contributing factors	Potential tests/ interventions	Nursing considerations
Pulmonary embolism. *A 37-year-old female with myosarcoma currently on treatment presents with sharp left-sided chest pain and SOB since 0800 today. She has a past medical history of right deep vein thrombosis. The pain worsened with motion and deep breathing. The pain has been progressively increasing in severity and she now has severe left back and shoulder pain. She complains of SOB and "feels like she is going to die." She denies cough, fever, sputum production, or hemoptysis*				
BP 121/84 HR 121 T 37.2 R 25 SpO_2 89%	Symptoms and clinical presentation may vary depending on the size of embolus & preexisting cardiopulmonary status, including asymptomatic/ incidental findings via outpatient diagnostic imaging studies Chest pain, often angina type onset and worsens with deep breathing. Chest pain will progress to pleuritic Dyspnea with sudden onset, tachypnea, crackles/wheezes, diminished breath sounds Tachycardia Low-grade fever (~40% of patients with PE) Cough/hemoptysis Syncope Back or abdominal pain Diaphoresis	Venous stasis Coagulopathies (may be induced by therapy or disease process) Atrial fibrillation Increased fatigue/ decreased activity Lung disease	General labs ECG Oxygen support CT with contrast to identify PE Arterial blood gases D-dimer (not as specific in cancer population) Initiation of thrombolytic therapy	Teach self-injection of low molecular weight heparin Monitor cardiopulmonary status for changes/ deterioration, may be rapid onset IV catheter = 18 g minimum for chest CT PE study protocol
Pleural effusion. *A 68-year-old man with lung cancer, congestive heart failure, and a 40-year history of cigarette smoking two packs a day. The patient reports that he has stopped smoking because of the lung cancer diagnosis. The patient presents to ED with shortness of breath and right-sided chest pain that worsens with deep breathing.*				
BP 150/70 HR 104 T 36.6 R 26 SpO_2 86%	Signs/symptoms dependent on amount and rate of fluid accumulation Dyspnea Cough Chest discomfort Abnormal breath sounds/ presence of pleural friction rub	CHF Pneumonia Malignancy Pulmonary embolism Pericardial constriction Obstruction of pulmonary vessels by tumor or stenosis Shedding of malignant cells into pleural space	General labs Chest X-ray and/or CT scan VQ scan ABG Thoracentesis provides symptomatic relief May be eligible for discharge if thoracentesis provides relief Cytological analysis of pleural fluid to determine if malignant cells are present	Information about procedure Treatment plan and possible placement of self-managed drainage system for recurrent pleural effusions Follow-up plan for early diagnosis and intervention for recurrent pleural effusion
Pneumonia [17, 18]. *A 68-year-old man with prostate cancer presenting to ED with a productive cough, fever × 3 days, shaking, and chills. He describes the sputum as thick and yellow. He also adds that a day ago, he developed pain in his right chest that is worsened with inspiration.*				

(continued)

Table 6.1 (continued)

Vital signs	Signs and symptoms	Risk factors/contributing factors	Potential tests/ interventions	Nursing considerations
BP 92/53 HR 120 T 39.0 R 26 SpO_2 90%	Fever, cough, sputum, hypoxemia, SOB Back pain, based on location of consolidation Vague, ill-defined symptoms Fatigue	Neutropenia Decreased activity Chronic obstructive pulmonary disease	General labs Blood cultures Lactic acid IV antimicrobial therapy Fluid resuscitation, ensure adequate cardiac status Sputum cultures Supplemental oxygen and use of noninvasive ventilation	Sepsis protocol Monitor changes in respiratory status, reposition as appropriate Maintain patent airway Promote normothermia Optimize fluid balance Encouraging coughing and deep breathing Promote adequate nutrition
Pneumothorax. *A 68-year-old female with a large tumor in the right lung presents with sudden onset shortness of breath. She is in acute distress and is breathing rapidly. Breath sounds are absent on the right.*				
BP 96/57 HR 119 T 38.6 R 27 SpO_2 88%	Signs/symptoms dependent on size/location of pneumothorax Respiratory distress/failure Dyspnea and chest pain Absent or decreased breath sounds on affected side Pneumothorax hyperresonant by percussion Deviation of trachea Unequal chest expansion Hypotension	Pulmonary malignancy Previous pneumothorax Procedures (i.e., central line insertion) Rupture of necrotic neoplastic tissue in pleural cavity [19] Tumor at lung periphery [20–22] Oncologic therapy [23]	Chest X-ray/CT scan Ultrasound Identification and treatment of underlying cause; may not require intervention Chest tube insertion	Monitor changes in respiratory status Assistance with chest tube insertion and management Pain management
Deep vein thrombosis. *A 54-year-old woman with uterine cancer and currently on treatment presents with left leg pain and swelling. She also reports that the swelling has been increasing over the course of 1 week. The affected leg is warm to touch, red, and edematous.*				
BP 152/74 HR 74 T 36.8 R 18 SpO_2 96%	Tight ache, tight feeling, or frank pain in calf or behind knee aggravated with standing or walking; alleviated with elevation Localized tenderness or pain over involved vein Tender, palpable venous cord of involved vein Swollen calf or thigh by measurement Calf swelling more than 3 cm in circumference in symptomatic leg Unilateral pitting edema in involved extremity Dilated superficial venous collateral vessels (non-varicose) Low-grade fever is possible	Procedures causing venous stasis (lengthy surgery) Active cancer (treatment or palliation within previous 6 months) Hypercoagulable state causing factors (physiological, environmental, iatrogenic) Presence of intravenous device (central venous access device) Coagulopathy induced by malignant cells Venous stasis (clot formation; pooling) Damage to blood vessel wall (endothelial)	General labs Laboratory: D-dimer Prothrombin/PTT Doppler ultrasonography Treatment: anticoagulants Surgical intervention: placement of vena cava filter to prevent PE in recurrent DVT Low-molecular-weight heparin (LMWH) may be self-administered	Minimize or prevent respiratory compromise Understand condition (signs & symptoms), risk factors, prevention and management Preventing further harm (adherence to treatment regimens, diet consistent with prescribed medication, health promotion) Safety measures: avoid contact sports, use of soft toothbrush for oral care and electric razor if there is a need to shave Monitor for changes and report leg pain, bleeding or signs of thrombophlebitis or PE
Pericardial effusion and cardiac tamponade [24, 25]. *A 55-year-old female with AML, currently on treatment, presents to the ED with complaints of a syncope episode with no injury. She endorses loss of consciousness for approximately "5 seconds" (verified by his adult son who was present at the time of fall). She reports that for the last 2 days, she has experienced increased fatigue associated with SOB. On assessment, her heart sounds are muffled on auscultation.*				

Table 6.1 (continued)

Vital signs	Signs and symptoms	Risk factors/contributing factors	Potential tests/ interventions	Nursing considerations
BP 108/60 HR 118 T 37.1 R 18 SpO_2 94%	Hoarseness, cough, hiccups, difficulty swallowing (compression of trachea, esophagus, vagal nerve) Muffled heart sounds Pericardial friction rub may be heard Increased jugular venous distension Kussmaul respirations Narrowing of pulse pressure – systolic blood pressure decreases and diastolic increases Paradoxical pulse (decline in systolic blood pressure on inspiration) Other signs of decreased cardiac output include tachycardia, anxiety, restless, peripheral cyanosis, oliguria, shock	Tumors most often associated with pericardial metastasis Some primary tumors (rare): sarcomas and mesotheliomas Lung and breast cancers can spread by direct extension of lymphatic metastasis Lymphomas and Leukemia routinely spread by hematogenous routes Radiation therapy of >4000 rad to the mediastinum Accumulation of excessive fluid within the pericardial sac (pericardial effusion) increasing pressure and compressing the heart	Primary goal to remove fluid and relieve/prevent impending cardiac collapse Chest X-ray, CT ECG Echocardiography Percutaneous pericardiocentesis Pharmacologic management to control heart rate	Patient teaching: early identification of signs/ symptoms Maximize safety with activities of daily life and ambulation Intervention to minimize severity: elevate head of bed; oxygenate; and manage pain and dyspnea Measures to enhance adaptation and rehabilitation

Patients undergoing cancer treatment may also reduce their activity, placing them at higher risk of developing thrombosis, leading to pulmonary emboli. The patient may be asymptomatic but should be treated with daily injections of anticoagulants. It is important to evaluate the patient's clotting times and platelet counts, as this may exclude them as candidates for anticoagulation therapies [30].

Chief Complaint: Altered Mental Status

Altered mental status (AMS) is a frequent chief complaint in oncologic patients presenting to the ED [31]. These mentation changes can result from metabolic disturbances, structural changes (such as metastatic disease or intracranial hemorrhage), or infection [32]. Ruling out the most life-threatening conditions is critical, as interventions are time-sensitive and require prompt identification to achieve desirable outcomes [33]. Table 6.2 illustrates presentations involving altered mental status [34–45].

Patients may present with varying degrees of AMS based on causative factors [32]. They may present as confused, somnolent, inattentive, or with seizure activity, both focal and widespread. Consider the type of cancer, risk factors associated with metabolic changes, infection risk, metastatic disease, and bleeding risk. Associated presenting symptoms and vital signs will also assist in identifying the underlying cause. Obtaining a thorough history from a family member or caregiver may also provide relevant information to AMS's cause, including the onset of mentation change, medications, medical history, and significant events. While the presence of malignancy creates an increased likelihood of atypical differential diagnoses, it is important to consider still acute ischemic stroke, hypoglycemia, and other common underlying conditions for patients presenting with changes in mentation.

Most oncologic patients presenting to the ED with AMS should receive a STAT head CT to determine if there is hemorrhage, as oncologic patients on active treatment are at higher risk for thrombocytopenia leading to bleeds [33]. Additionally, patients with known brain metastases are at risk due to the highly vascular nature of neoplasia. In addition to diagnostic imaging, a CBC and comprehensive metabolic panel (CMP) should be obtained. Platelets and white blood cell count may indicate additional causes, such as bleeding or infection. Many treatments cause pancytopenia and electrolyte disturbances that may be relevant to the patient's condition. Disturbances in electrolytes, bilirubin, and ammonia may cause changes in mentation. For example, hypo and hypernatremia can cause significant mental status changes and a common metabolic disturbance in certain lung cancer types. Ammonia can also cause AMS and may be present in cancers with hepatic involvement. All these components of the initial workup will assist in identifying the cause of AMS.

In the presence of new metastases identified in diagnostic imaging, corticosteroids can reduce edema around the lesion and subsequently diminish AMS symptoms [46]. If an acute ischemic stroke is suspected, it is critical to verify the platelet count to determine if the patient is an appropriate candidate for

Table 6.2 Case studies: altered mental status

Vital signs	Signs and symptoms	Risk factors/ contributing factors	Potential tests/ interventions	Nursing considerations
AMS related to metastatic disease [34]. *A 50-year-old female with history of breast cancer with bone/liver metastases presenting with altered mental status. Her boyfriend states she has increased confusion over last few days. He states she is not answering questions appropriately and has not been taking her medications as directed. Patient oriented to person and place but does not know what year it is. She is inattentive and takes a long time to respond to simple questions.*				
BP 117/68 HR 84 T 37.0 R 16 SpO_2 98%	Confusion (may be intermittent) Somnolence Seizures (may be focal)	Metastatic breast cancer Breast cancer has high metastatic risk in late stages	CT head Steroids (dexamethasone) Emergent neurosurgery to alleviate intracranial pressure if causing edema or ventricular obstruction	Frequent neuro vital signs Around the clock steroids to avoid additional edema Notify provider of any changes in mental status from initial baseline Elevate HOB and promote proper body alignment
AMS related to metabolic disturbances – sodium [35–40]. *A 56-year-old male with small-cell cancer of right lung, metastatic disease to bone/brain. He presents with altered mental status exhibiting delayed responses, confusion, and decreased concentration. Oriented to place/person but not time, GCS eye 3, verbal 4, and motor 6.*				
BP 117/68 HR 124 T 37.0 R 16 SpO_2 98%	Confusion Decreased PO intake Fatigue	Small cell lung cancer Most common electrolyte abnormality with small-cell lung cancer is hyponatremia Advanced disease increases likelihood of metabolic complications	General labs Head CT scan r/o bleed or metastatic progression Sodium replacement	Rebound cerebral edema with hypertonic solutions Seizure precaution Frequent neuro vital signs to identify subtle changes
AMS related to metabolic disturbances – ammonia [41–45]. *A 49-year-old female with metastatic colon cancer presents with altered mental status. Oriented to self only. GCS eye 4, GCS verbal 5, GCS motor 6. Patient has a history of hyponatremia, hyperkalemia, liver metastases. Finger stick glucose 105 mg/dL.*				
BP 93/58 HR 82 T 36.4 R 18 SpO_2 98%	Aggressive Confusion Lethargic Dehydration Hypotensive	Duodenum adenocarcinoma Cirrhosis of the liver Three cycles of chemotherapy Kidney damage and/or liver damage Drug, alcohol abuse Chemotherapy Colon cancer Liver failure	CBC, CMP, UA/C, PT/PTT, ammonia, liver enzymes CXR, EKG, CT head to r/o bleed Fluid resuscitation to flush Lactulose	Place on seizure precautions Monitor cognitive facilities May need restraints if aggressive If patient is unconscious, may have to administer lactulose through NG tube or rectal Lactulose will induce diarrhea and can contribute to falls

tissue plasminogen activator (tPA) [47]. If an infection is suspected, the patient should promptly receive broad-spectrum antibiotics. Timely administration of antibiotics can significantly improve patient prognosis in the presence of sepsis, with AMS being a frequent symptom indicating infection [48]. Patients with metabolic imbalances will improve upon the correction of the underlying disease process. Neurosurgery or neurology services may be consulted to address any neurological interventions based on ED findings [49].

Throughout the ED encounter, the EN should perform frequent neuro assessments to detect early deterioration signs. Placing the patient in semi-fowlers, elevating the head of the bed to 30 degrees or higher, and ensuring proper body alignment may also benefit patients with increased intracranial pressure [50]. Any changes in status should be immediately communicated with the provider. If steroids are ordered, they should be administered at scheduled times to reduce associated edema [49].

Chief Complaint: Back Pain

While back pain is a common chief complaint in EDs, the presence of back pain with cancer diagnoses can indicate metastatic spinal cord compression (MSCC), a time-sensitive emergency that requires prompt intervention. Although back pain is the most common complaint with MSCC, patients may also present with numbness, pain, or tingling in their extremities, bowel or bladder retention or incontinence, and even paralysis or gait disturbances. Patients with breast, lung, prostate, and renal cancer, as well as lymphomas and myelomas are at the highest risk, with men outnumbering women 2:1 [51]. See case study in Table 6.3 [51, 52].

Presenting symptoms will depend on the level of involvement and the degree to which the metastatic lesion is invading the spinal column. The degree of vertebral lesion invasiveness directly correlates with symptom severity. Symptoms may be alleviated with steroids by reducing the pressure on the spinal column [53]. Although symptoms may improve, these patients are at high risk for falls due to sudden sensory and motor function disturbances [54]. The patient's position may influence symptoms, activity level, level of involvement, and lesion location. Identifying a patient's position that reduces pain is important, and those with severe pain should be log rolled to avoid further injury. Range-of-motion assessments should also be conducted with caution, as they can cause additional injury in the presence of osteolytic lesions. These patients are at high risk for spinal instability, pathological fractures, and caudal equine syndrome.

Assessing for urinary retention and post-void residual are also necessary to determine if urinary catheter placement is necessary. Although patients may feel that they have fully emptied their bladder, there may be significant post-void residual, causing additional complications if not completely emptied. Patients may not state any bladder or bowel malfunctions due to loss of sensory perceptions, so assessment is necessary, regardless of patients' perceptions.

The radiological imaging modality of choice is magnetic resonance imaging (MRI) without contrast. If the patient cannot tolerate an MRI, a CT or X-ray may reveal findings but are not sensitive [55]. Treatments may include corticosteroids, radiation therapy, surgical intervention, and palliative chemotherapy [56]. Spinal cord metastases indicate late stages of cancer, and depending on patient functional status, treatment focus may be symptom management. Patients with MSCC may be candidates for advance care planning conversations, as this condition indicates advanced disease and poor prognosis [57].

Chief Complaint: Abdominal Symptoms

For patients with a concurrent cancer diagnosis, abdominal symptoms may indicate a variety of medical emergencies. Table 6.4 illustrates a number of presentations associated with these symptoms [58–80]. Oncologic patients are at high risk for bowel obstruction due to medication and antineoplastic treatments. Without prompt gastric decompression or surgical intervention, this can progress to perforation and severe infection. These patients may also present with nausea and vomiting due to the obstruction [81].

Table 6.3 Case study: back pain

Vital signs	Signs and symptoms	Risk factors/ contributing factors	Potential tests/ interventions	Nursing considerations
Metastatic spinal cord compression [52]. *A 67-year-old male with a history or metastatic prostate cancer presents to the emergency department with lower back pain 8/10 that has been progressing over the last week. He states he has some tingling in his legs and feels weak when he is ambulating.*				
BP 130/82 HR 77 T 36.8 R 16 SpO_2 97%	Primary complaint = back pain Weakness Paraplegia Sensory disturbances (numbness, neuropathy) Autonomic disturbances (incontinence, urinary retention)	Men out-number women 2:1 [51] Most prevalent in breast, lung, prostate, renal, lymphoma & myeloma Caused by vertebral body metastasis invading the spinal column Level of involvement directly reflects functional status and clinical presentation Symptoms may be affected by positioning (i.e., sitting vs. standing vs. laying down)	Diagnostics: radiological imaging of choice = MRI without contrast CT or X-ray if patient unable to tolerate MRI, not as sensitive Assessments: serial neurological evaluations, post-void bladder scan Treatments: corticosteroids, radiation therapy, surgical intervention, chemotherapy	Post-void bladder scan to evaluate for urinary retention Avoid range-of-motion testing if concern for spinal instability Best to immobilize patient as much as possible to prevent pathological fractures or additional pressure on the spinal cord High fall risk Strict bed rest for patients with poor performance status or spinal cord instability Indicates advanced disease = warrants advance care planning conversation

Table 6.4 Case study: abdominal symptom

Vital signs	Signs and symptoms	Risk factors/contributing factors	Potential tests/ interventions	Nursing considerations
Bowel obstruction [58–61]. *A 66-year-old female with a history of ovarian cancer presents with severe abdominal pain (9/10). Pain has progressed and began 4 days ago. She has a history of abdominal surgery, followed by radiation and chemotherapy treatment for her ovarian cancer. She has known metastatic peritoneal disease. Patient has not had a bowel movement in 5 days and feels nauseated. Chronic opioid use for pain related to cancer pain and radiation.*				
BP 146/90 HR 106 T 37.8 R 22 SpO_2 96%	Abdominal pain, cramping, distention Nausea and vomiting Loss of appetite Constipation and inability to pass gas	Previous abdominal surgery and scar tissue History of colon or rectal cancer or from other organs that has spread to the abdomen Inflammatory bowel disease Diverticulitis Previous abdominal or pelvic radiation Radiation and previous abdominal surgery Opioid induced constipation Age Intra-abdominal lesions and surgical scarring	General and coagulation labs Abdominal imaging Nasogastric tube insertion for decompression Antibiotics, fluids, pain control Possible surgery	Monitor for changes, if bowels perforate may quickly progress to sepsis Neuro checks Support B/P Possible sepsis NPO Pain management Strict I&O (Foley) Fall risk
Diverticulitis [62, 63]. *A 52-year-old white female history of melanoma, diverticulosis, and constipation with recent chemotherapy. The patient complains of abdominal pain in the lower left side over the past week progressively getting worse last night. Her pain level is 7/10.*				
BP 160/88 HR 94 T 38.0 R 20 SpO_2 97%	Pain lower left side of abdomen progressively getting worst over the last 5 days Nausea and vomiting Fever Abdominal tenderness, cramping Constipation	Advanced age Obesity Smoking Diet high in animal fat and low in fiber Certain medication Genetics Diverticulosis Immunocompromised Constipation	CT scan of the abdomen and pelvis, CBC, chemistries Rest, oral antibiotics, liquid diet More severe IV antibiotics, hospital admission, surgery Mild case may be discharged home if able to tolerate PO	Pain management Hydration GI rest clear liquids Nutrition education high-fiber diet, starting with low fiber initially
Gastrointestinal bleeding [62, 64]. *A 72-year-old Hispanic male with esophageal cancer presents to the ED with abdominal pain over the last month and hematemesis this morning, reports black tarry stools and weakness progressing over the last week. History of pulmonary embolism 2 months ago, on coumadin.*				
BP 82/50 HR 121 T 36.0 R 20 SpO_2 97%	Hematemesis Black tarry stool, rectal bleeding in or with stool Abdominal pain Weakness Low blood pressure	History of peptic ulcer disease or GI bleed Advanced age NSAID, anticoagulants Esophagitis IBD, colon polyps, hemorrhoids, diverticular disease, proctitis, anal fissures Esophageal tumor	CT scan of abdomen and pelvis with IV contrast CBC, PT with INR, PTT, D Dimer, fibrinogen, type and screen, CMP, magnesium, phosphorus, amylase, lipase, UA, urine culture EKG 12 lead, FOBT, endoscopy, colonoscopy, angiography Cardiac monitoring May be given PPI, may be taken off blood-thinning medications, pain medication	Assess for bleeding in stool ECG Strict I&O Administer pantoprazole Monitor heart rate and blood pressure Monitor H&H and clotting times Assess patient history and medications Support

Table 6.4 (continued)

Vital signs	Signs and symptoms	Risk factors/contributing factors	Potential tests/ interventions	Nursing considerations
Diarrhea [65, 66]. *A 35-year-old Asian female with breast cancer presents with 2 days of watery stool, abdominal cramping, and low-grade fever. She received chemotherapy approximately 3 days ago and feels weak and exhausted. Her primary oncologist recommended she come to the ED.*				
BP 102/58 HR 107 T 37.9 R 18 SpO_2 96%	Abdominal pain Watery stool Fever Abdominal distention	Viruses, bacteria, parasites Medications, including chemotherapy Graft versus host disease Lactose intolerance Surgery Recent chemotherapy Infection Food contamination	CBC, CMP, magnesium, phosphorus, stool culture, stool for C-diff, FOBT, colonoscopy Antibiotics, adjusting medications being taken Treatment plan to replace lost fluids and electrolytes Observation pending test results May discharge home after hydration and diarrhea resolves	Assess for abdominal discomfort, loose stools, cramping Inquire about: tolerance to milk and other dairy products, food preparation, medications patient is or has been taking, and current stressors Check for history of abdominal radiation, GI diseases, foreign travel, and drinking untreated water
Constipation [67, 68]. *A 76-year-old male with sigmoid adenocarcinoma presents seeking treatment for increasing abdominal pain and constipation persisting for 3 weeks. He is on Oxycontin. The patient complains of passing dry, hard stool every 5 days and a desire to defecate. Strains without relief after having a bowel movement.*				
BP 168/88 HR 86 T 36.9 R 18 SpO_2 98%	Dry hard stools Passing fewer than 3 stools a week Straining to have bowel movements Abdominal pain	Age Diet low in fiber Little to no physical activity Taking certain medications including sedatives, opioid pain medications, antidepressants or medications to lower blood pressure Cancer Poor hydration	CBC, chemistries CT of abdomen and pelvis, colonoscopy, X-ray, anorectal manometry, defecography (outpatient) Increase fiber intake, increase exercise, prescription medication and laxatives Surgery Admit to observation Discharge home if able to provide relief with enema/medication and CT negative	Classify medication usage that may lead to constipation Assess patient's activity level Assess patient's diet and eating habits Check frequency and consistency of stool Check for history of neurogenic diseases
Nausea and vomiting [69–71]. *A 40-year-old African American female with uterine carcinoma on active treatment presents to the ED complaining of nausea and vomiting. She has vomited 4 times in the last hour and is unable to keep anything down orally. Her nausea is increased with certain smells.*				
BP 95/60 HR 116 T 37.1 R 20 SpO_2 96%	Nausea and vomiting Weakness and fatigue	Cancer treatment Emotional distress Medication Gender BMI Motion sickness History of migraine Tumor Obstruction	CT abdomen/pelvis w/ contrast General/abdominal labs EKG, cardiac monitoring Clear liquids IV hydration Electrolyte replacement Antiemetics Patient may be managed at home with instructions and antiemetics as needed if improves and test are negative	NPO, may progress to clear liquids with PO challenge Assess medications that may lead to nausea/ vomiting Asses abdomen for distention and cramping, frequency of vomiting and emesis contents Strict I&O Fall risk

(continued)

Table 6.4 (continued)

Vital signs	Signs and symptoms	Risk factors/contributing factors	Potential tests/interventions	Nursing considerations
Urinary retention [72–76]. *A 73-year-old male with bladder cancer and suprapubic catheter presents with urinary retention for 3 days and abdominal pain worsened by tactile pressure.*				
BP 166/90 HR 106 T 36.8 R 20 SpO_2 94%	Acute suprapubic pain Anuria Distended bladder Urgency	Benign prostatic hyperplasia Bladder cancer Hemorrhagic cystitis History of hypertension and diabetes mellitus Increased age Affects men more than women Postop complication (s/p TURP) Medication related Blockage (stone, mass) Urinary tract infection Abscess Inflammation (cystitis, urethritis) Pelvic radiation Cord compression Penile trauma Fecal impaction	Bladder scan, CBC, CMP, UA/UC, indwelling catheter placement Medication for bladder spasm (hyoscyamine) Antibiotic for UTI Urology consult	Assess for previous surgeries/trauma/tumor Place catheter, preferably 16Fr or large enough to pass blood clots for that is determined to be the issue, may have to use coudé tip if patient has enlarged prostrate Consult urology if unsuccessful with catheter placement Monitor patient for electrolyte abnormalities, dehydration, hypotension after rapid bladder decompression Maintain adequate fluid intake
Acute kidney injury [77]. *A 65-year-old male with prostate cancer and chemotherapy 2 days ago presents to the ED with asymptomatic abnormal elevation of creatinine from routine office appointment.*				
BP 122/80 HR 76 T 36.9 R 16 SpO_2 97%	Leg swelling Potassium 6.7 Creatinine 8.32	Bladder cancer Nephrotoxic medications, including chemotherapy Obstructive hydronephrosis (tumor, clot)	Repeat labs, CBC/CMP, BUN UA, serum and urine electrolytes EKG and cardiac monitoring Renal ultrasound Fluid resuscitation Renal consult Possible surgical intervention (percutaneous nephrostomy) Kayexalate, albuterol nebulizer, 10 units insulin, calcium gluconate, 1 amp, D25, bicarb 50 meq	Review medications to discontinue nephrotoxic medications Anticipate adjusted medications according to renal function Monitor pulmonary and cardiovascular events due to fluid overload and electrolyte imbalances Monitor I/O Monitor changes in mental status Complications of acute kidney injury in cancer patient may limit the patient's ability to continue treatment Monitor blood glucose before and after insulin dose
Hematuria. *A 79-year-old male with bladder cancer and renal cancer presents to the ED with complaint of lower abdominal pain and blood in urine for the past 12 hours. The patient was seen at an outside facility and found to have creatinine 2.4, pyelonephritis, and cystitis.*				
BP 164/74 HR 90 T 36.5 R 20 SpO_2 90% (on 2 LPM via nasal cannula)	Hematuria Blood clots Urinary retention Pain	Bladder, urethral or kidney cancer UTI Trauma (pelvic area, renal) Hemorrhagic cystitis Pelvic radiation Chemotherapeutic agents (ifosphamide, cyclophosphamide) Medications Nephritis Calculi Renal cysts Enlarged prostate (causing to strain and rupture vessels)	Labs (CBC, CMP, UA/UC), adequate fluid intake Continuous bladder irrigation Diagnostic imaging (renal U/S, cystoscopy) Antibiotics for treatment of UTI Urology consult	Bladder irrigation via 3-way catheter, titrate drip to light pink, almost clear output, continuous irrigation If interrupted, clot may form If leaking at catheter insertion site, catheter most likely blocked with blood clot and clot will need to be irrigated May have to use coudé tip catheter if patient has enlarged prostate. Monitor hemoglobin and electrolytes

Table 6.4 (continued)

Vital signs	Signs and symptoms	Risk factors/contributing factors	Potential tests/ interventions	Nursing considerations
Bile duct obstruction [78–80]. *A 72-year-old female with pancreatic cancer on active treatment presents to the ED with vomiting and fatigue for the past week. She is jaundiced and slightly confused. She states she has generalized pruritus and abdominal cramping.*				
BP 104/66 HR 76 T 36.9 R 16 SpO_2 99%	Projectile vomiting Upper right abdominal pain Lethargy, anorexia/decrease in appetite Severe heartburn/ reflux	Pancreatic cancer Female Increased age Diabetes mellitus Type II	General labs, bilirubin, alk phos, liver enzymes CT scan GI endoscopy consult for stent placement or G-tube placement	If undergoing biliary drainage patient should receive broad-spectrum antibiotics within 1 hour of start of procedure due to transit bacteremia during or after the procedure Monitor for bleeding, leakage around the tube and subsequent skin breakdown, catheter related pain, pancreatitis, sepsis

Cancer-related treatments may also cause acute kidney injuries (AKI) present as abdominal pain, oliguria, and flank pain. Depending on cancer location and gastrointestinal involvement, disease progression may be the primary factor causing pain or obstruction. Location of the pain, severity, onset, aggravating and alleviating factors, as well as medical and oncologic history is important in determining the cause of abdominal pain and necessary interventions. Due to pancytopenia caused by many treatments, bleeding and infection should also be considered if indicated in clinical presentation [81].

Unfortunately, cancer treatment frequently causes nausea and vomiting. Prevention of dehydration and symptom management are most important in chemotherapy-induced nausea and vomiting and depending on the severity, patients may require scheduled administration of multiple antiemetics. Sensations, including smell and taste, are also impacted with chemotherapies, and something as innocent as perfume may trigger emesis. Nurses should avoid wearing any creams, lotions or perfumes with strong scents that may trigger episodes of nausea and vomiting [82]. When attempting oral intake, small volumes of plain food and drink are best, as foods with strong flavors or smells may also increase the risk for emesis or even aspiration. Additionally, elevating the head of the bed to prevent aspiration is an important safety measure, as vomiting episodes may be sudden without warning [83].

In addition to upper GI symptoms, cancer treatments can cause lower GI symptoms such as constipation and diarrhea. Severe constipation can develop with both treatment and symptom management therapies, such as opioids for pain management. All cancer patients should be on a stool softener to prevent fecal impaction that can lead to additional complications. Before administering an enema, platelet levels should be verified to ensure no bleeding risk. In cases of diarrhea, dehydration can quickly progress and electrolyte imbalances may occur. Prompt replacement of fluids and electrolytes is necessary to prevent further complications related to electrolyte deficiency. While treatments can induce adverse events, patients with previous stem-cell transplants may experience similar symptoms due to graft-versus-host disease (GVHD). In these cases, tacrolimus levels should be monitored and steroids are generally the treatment of choice [84].

Ascites and abdominal distention are commonly seen in patients with metastatic peritoneal disease. Ascites may be recurrent and require frequent removal of peritoneal fluids via paracentesis. For patients with recurrent ascites due to metastatic disease, a peritoneal drain may be indicated to allow the patient to self-drain fluid build-up in the abdomen and prevent frequent ED visits. Patient education and discussion with the primary oncologist will help determine if the patient is an appropriate candidate for peritoneal catheter placement [85].

With cancer patients being at high risk for infection, the presence of colitis, gastritis, and diverticulitis should also be assessed to determine if a patient requires antibiotic therapy. Infection should always be addressed in any cancer patient presenting with abdominal symptoms to prevent further deterioration [81].

Abdominal symptoms are common for both general ED patients and cancer patients and are caused by various conditions. The patients' medical and oncological history can guide patient diagnoses, including cancer type and associated events leading up to the ED encounter. Evaluation of laboratory findings, including hepatic functions, pancreatic enzymes, CBC and CMP, is also essential in determining an appropriate treatment course.

Chief Complaint: Infection

Many cancer patients undergoing treatments experience pancytopenia, including neutropenia. This places them at significantly higher risk for developing an infection and becoming septic. Patients may present initially with a fever and neutropenia and otherwise stable vital signs. That said, these patients have a minimal metabolic reserve and no immune defense mechanisms, so they can quickly decline without the initiation of appropriate interventions. A central line is frequently standard in patients receiving chemotherapy regimens. This direct access to the bloodstream also places patients at higher risk for bacteremia and sepsis [86].

Development of a sepsis protocol and standing parameters for early interventions can help decrease the time from door to antibiotic administration, resulting in more favorable outcomes. Once the infection source is identified, antibiotic therapy should be tailored based on the organism's susceptibility to promote antibiotic stewardship [87].

Patients presenting with fever can be quickly identified as having a potential infection or sepsis. Some patients experience a condition called "tumor fever," which is the most frequent cause of pyrexia unrelated to infection. This is most commonly present in leukemias, lymphomas, sarcomas, renal cell carcinomas, and patients with liver metastases, but may present in any type of cancer. Although the cause may be unknown, patients should be treated as if an infection is present until otherwise ruled out [88].

There are some cases where patients are afebrile but exhibit tachycardia, tachypnea, or hypotension. These may indicate infection but are nonspecific in cancer patients. These could be caused by many other conditions common in cancer patients, including anemia, dehydration, or different physiological responses to malignancy. Infection is frequently the culprit in these cases, but does not rule out other diagnoses. Additionally, ED nurses should identify if the patient is taking any medications that could reduce the temperature before ED arrival, such as acetaminophen or ibuprofen. This may mask the fever and cause infection to be overlooked [88]. Table 6.5 illustrates typical presentations for neutropenic fever and sepsis [89–93].

Chief Complaint: Newly Diagnosed Cancer in the Emergency Department

Although less common, patients may present to EDs without a cancer diagnosis, only to be diagnosed during treatment in the ED [94]. These situations can be high acuity and high stress, as the patient's medical management may be complicated, and the emotional stress of the patient and family will likely be heightened. The initial presentation will vary based on underlying cancer diagnosis but may range from nonspecific complaints to a growing tumor site. Regardless of the final cancer diagnosis, the patient and family will need significant psychosocial support to begin their journey as cancer patients [95].

For patients without established primary care, the ED may be their only access to medical services. Unfortunately, patients presenting with an invasive solid tumor without

Table 6.5 Case studies: infection

Vital signs	Signs and symptoms	Risk factors/ contributing factors	Potential tests/ interventions	Nursing considerations
Neutropenic fever [89]. *A 52-year-old female currently undergoing treatment for recent diagnosis of AML presents with fever of unknown origin. History of stage III breast cancer; treatment completed 2 years ago. White blood cell counts this morning showed absolute neutrophil count (ANC) < 500.*				
BP 98/68 HR 104 T 39.2 R 20 SpO_2 94%	Fever Fatigue	Poor performance status Advanced oncologic disease Low blood cell counts Chemotherapy Hematologic cancers Opportunistic infection	CBC with diff Blood culture Broad-spectrum antibiotics	Timely administration of antibiotics to prevent further deterioration and sepsis cascade
Sepsis [90–93]. *An 86-year-old female presents with fever, SOB, fatigue. She states she has back pain worsening over past 24 hours. Had chemotherapy for Stage III breast cancer approximately a week and a half ago. She has a double lumen peripherally inserted central catheter (PICC) line in her right arm.*				
BP 77/47 HR 127 T 38.9 R 24 SpO_2 89%	Hypotension Tachycardia Fever	Central venous access Neutropenia - nadir from chemotherapy Increased age Chemotherapy Hematologic cancers	CBC with diff Blood cultures Lactic acid Broad-spectrum antibiotics	Sepsis mortality increases Poor tissue perfusion

prior cancer diagnosis tend to have a poor prognosis. Patients diagnosed with cancer in the ED are usually in late stages of the disease, with a 75% higher risk of being diagnosed as stage 4 cancer, versus stage 1 [96]. These patients may not have access to healthcare in a primary care setting, causing them to utilize the ED for access to treatment. Patients may not have symptoms severe enough to prompt an ED encounter until cancer has progressed. Delays in cancer diagnosis significantly increase the likelihood of metastatic disease being present upon initial diagnosis. Because of the poor prognosis, advance care planning should be discussed with the patient and family to ensure the quality care that supports the patient and family's wishes. Generally, solid tumor patients will not require immediate antineoplastic therapy in an emergency setting. ED nurses should focus on symptom management, oncologic plan of care post-ED visit, and appropriate supportive services such as social work, case managers, nutritionists, and pain management specialists [96].

In contrast with solid tumors, different types of acute leukemias may present as a medical emergency and require prompt cancer treatment and immediate antineoplastic therapies. These cancers are frequently diagnosed in the ED and are sometimes only identified via blood work. Patients with acute leukemias tend to have nonspecific symptoms of infections. The proliferation of immature white blood cells causes insufficient immune defense mechanisms required to fight an infection, and this may be the only indication of the underlying issue. An analysis of blood work and subsequent bone marrow biopsy will identify the specific cancer type and appropriate treatments. These patients are at high risk for sepsis due to an ineffective immune system and coagulopathies due to increased blood viscosity and thrombocytopenia secondary to leukemia [97].

Patients with newly diagnosed leukemia should be regularly monitored for status changes, as they can quickly deteriorate. Those with a white blood cell count of 50,000 or greater will require immediate therapy to reduce the number of immature blasts in circulation. The type of cancer will determine the induction phase of treatment, which the ED nurse will likely initiate. Due to the high-risk and time-sensitive nature of induction therapies, protocols should be developed by both emergency and oncologic departments to ensure there are no administrative barriers that may prevent the patients from receiving immediate induction therapy in the ED. This collaboration between these specialties can be a significant factor influencing the patient's care course and subsequent outcome [97].

The ED nurse's role in newly diagnosed cancer patients is essential for their quality-of-life trajectory. Ensuring adequate education and resources can completely alter the patient's experience in the presence of a life-changing diagnosis, such as cancer. Although not all patients will be candidates for curative therapies, providing patients with all potential treatment options and plans of care will ensure they are on track for course best suited to their medical and psychosocial needs. Along with coordinating the various services, including patients and families, the care team should be prioritized by the ED nurse once medically stabilized [97]. Table 6.6 illustrates presentations for newly diagnosed acute myeloid leukemia and acute promyelocytic leukemia [98–105].

Chief Complaint: Malignancy Progression, Antineoplastic Treatments, and General Medical Emergencies

Complications may arise with patients throughout the course of their cancer diagnosis. These may arise both from disease progression and impact on physiological processes and antineoplastic therapies and the associated adverse effects. These can range from mild to severe, and a thorough patient medical history can help determine the underlying cause. As previously mentioned, treatments can cause pancytopenia resulting in anemia, thrombocytopenia, and neutropenia. These can lead to more severe complications such as infection or bleeding if not promptly addressed with the appropriate replacement or supportive therapy [106].

Disease progression will generally be related to the tumor's location and associated symptoms. Patients with primary or metastatic osteolytic lesions may develop pathological fractures as the disease progresses. These osteolytic lesions may initially cause the patient mild-to-moderate pain at the tumor site with an acute event producing a pathological fracture [107]. Patients with large abdominal or thoracic tumors can develop superior vena cava syndrome as the tumor grows, placing pressure on blood's systemic return to the heart. Certain neuroendocrine tumors can cause significant disturbances in hormonal and metabolic function, possibly resulting in diabetes insipidus, acute adrenal crisis (Addisonian crisis) and hypophysitis [108]. The tumor location and associated symptoms will greatly assist with determining differential diagnosis and appropriate treatments.

While cancer itself can produce adverse events seen in an emergency setting, the treatments patients receive can also have severe therapy-related adverse events. Patients who have received a stem-cell transplant (SCT) may also present with graft-versus-host disease (GVHD) complications. These can affect all organs and systems and are frequently treated with high-dose steroids [109]. Along with pancytopenia and associated conditions, many chemotherapies are nephrotoxic and cardiotoxic. Depending on the patient's ability to tolerate the treatment and underlying comorbidities, some patients may have more severe reactions than others [110]. Reviewing the patient's wallet insert that identifies

Table 6.6 Case studies: newly diagnosed cancer in the ED

Vital signs	Signs and symptoms	Risk factors/ contributing factors	Potential tests/ interventions	Nursing considerations
Acute myeloid leukemia (AML) [98–102]*: A 32-year-old male presents with abnormal lab results from his primary care provider who instructed his to present to the ED. The patient had an upper respiratory infection for 2 weeks that prompted him to see her PCP. PCP prescribed PO antibiotics and obtained a CBC. The patient has no significant medical history. CBC results showed WBCs 173 k, Platelets 4 k, Hgb 6.1. The patient is a smoker (1/2 per day) and works at a chemical plant.*				
BP 117/76 HR 107 T 37.7 R 18 SpO_2 97%	Frequently present after unresolved infection and discover abnormal blood counts May have weight loss, bleeding/bruising and fatigue due to counts	AML more common in males than females Risk factors for AML are exposure to certain chemicals (work exposure), radiation and smoking	General labs Hydroxyurea for leukocytosis Bone marrow biopsy PRBC and platelet transfusions to replace counts Chest X-ray to evaluate for potential pulmonary infiltrates Antibiotic and antiviral therapy to prevent infectious complications	High-risk for bleeding with thrombocytopenia Disseminated intravascular coagulation Highly viscous blood due to increased WBCs At risk for tumor lysis syndrome due to systemic cancer involvement
Acute promyelocytic leukemia (APL) [103–105]*. A 48-year-old male presents with low-grade fever, weight loss, increased fatigue, and increased bruising. The patient has worked at a crude-oil processing plant for 22 years and has no significant health history. Lab results show severe neutropenia, anemia, and thrombocytopenia*				
BP 110/68 HR 96 T 37.2 R 20 SpO_2 99%	Anemia Thrombocytopenia Neutropenia	Middle aged Long-term exposure to petroleum products Unknown May be associated with work exposure	General labs All-trans-retinoic acid (ATRA) Bone marrow biopsy PRBC and platelet transfusions to replace counts Chest X-ray to evaluate for potential pulmonary infiltrates Antibiotic and antiviral therapy to prevent infectious complications	High-risk cancer, but highly curable if treated timely Extremely rare subtype of AML Requires pathology evaluation of cell morphology to determine if APL versus other types of acute leukemia

the antineoplastic agent they are receiving may be beneficial. Obtaining this information as early as triage can help determine the differential diagnosis as well as medical management [110].

Dedication of resources to cancer treatment research has led to new therapies, emerging as first-line treatments producing promising outcomes. One of these recent advances is the increase of immunotherapies. Although these generally have a lower risk of associated adverse events, immunotherapies such as chimeric antigen receptor (CAR) T-cell therapy can induce specific emergent conditions, most frequently being cytokine release syndrome (CRS) and CAR-related encephalopathy syndrome (CRES). These emergent conditions may develop after receiving immunotherapies and must be treated timely to prevent long-term deficits. CRS and CRES have specific grading systems that should guide medical management and determine the severity of the condition [111].

Patients with cancer may have comorbidities, such as diabetes, hypertension, psychiatric conditions, cardiac dysrhythmias, and other chronic illnesses, and patients may present with conditions completely unrelated to their cancer or treatment. General medical emergencies such as ischemic stroke, myocardial infarction, or diabetic ketoacidosis (DKA) should still be considered, even in the presence of concurrent cancer, if the clinical presentation is consistent with the noncancer-related condition [112]. Notwithstanding, precautions should be taken when determining therapy for the medical emergency and how the patient's cancer may impact the typical course of management. For example,

patients exhibiting signs of ischemic stroke may not be candidates for tissue plasminogen activator (tPA) based on platelet count, coagulation studies, and bleeding risk. All factors should be considered when determining medical management for the patient. The ED nurses' role is imperative to ensure a holistic approach to patient care [113]. Table 6.7 illustrates the wide variety of patient presentations discussed above [114–144].

Chief Complaint: End of Life in Advanced-Stage Cancer

Although advances in oncologic treatments have greatly improved the overall survival rate of cancer, end of life, patients with advanced cancer disproportionately represent cancer-related visits to emergency departments. The high-acuity and fast-paced environment in the ED has been conventionally felt to be incompatible with end-of-life (EOL) discussions. The delicate topic is rarely addressed in EDs and can increase the psychosocial burden on the patient and family, increased costs, and futile care initiation. By providing a holistic approach and initiating conversations to establish care goals, the ED can help enhance the value and quality of care for EOL cancer patients [13]. Table 6.8 describes a typical presentation for a cancer patient presenting to the ED at the end of life [145–147].

Although the ED is not typically a setting where EOL discussions occur, initiating a palliative care (PC) consultation to assist with determining care goals with the patient and family member can greatly assist ED personnel in navigating the complex sequelae of the dying process in all domains [13]. Patients and families will require substantial physical, emotional, and spiritual support to ensure a smooth transition to hospice care. The ED nurse plays a central role in coordinating this care by ensuring all necessary services can provide expertise and guidance for the multifaceted needs associated with dying. These will include palliative, pain, hospice, nutrition, social work, case management, chaplaincy, and other multidisciplinary services based on the patient and family's unique needs. This experience can be the difference between a traumatic and peaceful death for both the patient and their loved ones [13].

As a gateway to hospitalization, the ED plays a vital role in the quality and value of EOL cancer patients' care. It is the tendency of ED personnel to choose life-saving interventions over meaningful conversations about advance care planning (ACP). EDs should ensure proper training and education are provided to staff to provide quality care and ensure dignity, compassion, and comfort for EOL patients. Altered mental status, dyspnea on minor exertion, and poor performance status (ECOG 3 or 4) were found in previous studies to be the "Triple Threat" predictors of mortality in advanced cancer. Patients with two or more of these conditions had a predicted 30-day mortality of 49% (95% CI. 34%, 64%) [145]. This may be used as a triage screening tool to identify advanced cancer patients who may benefit from care goals conversation.

In 2014, the Institute of Medicine (IOM) released the report, "Dying in America," calling for significant reform of the healthcare system to improve the quality and value of EOL care in America. The report cited recommendations to improve EOL care, including patient-centered and family-oriented EOL discussions, professional education and development of palliative care, healthcare policies to support EOL initiatives, and public education and engagement [148].

The National Quality Forum endorses multiple ED visits within the last 30 days of life to indicate poor-quality cancer care. Additional indicators of poor-quality cancer care include admission to the intensive care unit (ICU) within the last 30 days of life, death in the ICU, curative chemotherapy treatment in the last 14 days of life, and hospice admission for less than 3 days before death. ED nurses should advocate for EOL cancer patients to avoid poor-quality outcomes, enhance care value, and provide a positive experience for patients and families [148].

Ideally, these conversations would be initiated in an outpatient setting allowing ample time for discussion between providers, patients, and families. However, this is not always the case, and patients may only find out they are dying upon presentation to the ED. Although it may be perceived as challenging or inopportune, initiating a discussion of care goals in the ED can be one of the greatest gifts a nurse can provide to a patient [149].

Pandemic Response: SARS CoV 2 – Novel Coronavirus

Novel coronavirus disease (COVID-19), also termed SARS-COV-2, has emerged as a global threat and healthcare concern [150]. The virus first cases were reported in Wuhan, China, and marked the beginning of a global pandemic that completely upended daily life and the world's healthcare system [151]. Human-to-human transmission of COVID-19 occurs via respiratory droplets (by coughing or sneezing) and through direct contact with infected individuals or indirect contact with fomites of the affected individuals' environment [150]. Since its outbreak in China at the end of 2019 and until the April 5, 2020, the pandemic has affected > a million persons and caused 62,773 deaths worldwide [152].

Table 6.7 Case studies: malignancy progression, antineoplastic treatments, and general medical emergencies

Vital signs	Signs and symptoms	Risk factors/ contributing factors	Potential tests/ interventions	Nursing considerations
Cytokine release syndrome (CRS) & CAR-related encephalopathy syndrome (CRES) [114]. *A 61-year-old male presents to triage with tachycardia, hypotension, and shortness of breath. He received a chimeric antigen receptor T-cell (CAR-T-cell) therapy infusion for treatment of lymphoma approximately 3 days ago and was instructed to present to the ED.*				
BP 88/54 HR 126 T 37.2 R 20 SpO_2 89%	Looks a lot like sepsis Fever, myalgias, anorexia, evidence of multiple organ involvement (dyspnea, hypotension, arrhythmias, confusion seizures)	Recent CAR-T cell therapy infusion Liquid tumor, potential high tumor burden can cause increased cytokine release A therapy-induced immune systemic reaction Release of IL-6 proteins causes systemic inflammatory process	Tocilizumab is first line treatment Supportive therapy Rule out infection	CRS & CRES grading system Assess for CRES in the presence of CRS, may be concurrent Maintain $SpO_2 > 92\%$
Pathological fractures [115–117]. *A 55-year-old female with metastatic breast cancer with known bone metastasis. She has been experiencing right groin pain that started approximately 3 months ago and got significantly worse over the last 3 days. The patient is experiencing severe pain and is unable to bear any weight on her right leg, prompting her to present to the ED. The patient is slightly tachycardia (112), all other vitals are WDL.*				
BP 130/88 HR 112 T 37.2 R 18 SpO_2 95%	Pain, sometimes chronic with acute exacerbation Acute change in functional abilities of affected limb	Metastatic breast cancer to the bones Weight bearing activities on a bone that has a metastatic lesion	X-ray to evaluate for acute pathological fractures Orthopedic consult to evaluate for possible surgical reconstruction if patient is a candidate Pain control	Log-roll patients to avoid further injury Premedicate with analgesia prior to movement Stabilize with pillows to avoid positional exacerbation Be aware of other bone lesions and take extra precautions as appropriate
Diabetic Ketoacidosis (DKA) [118–120]. *A 64-year-old male undergoing treatment for prostate cancer with Lupron and prednisone. He presented to the ED with chief complaints of progressive weakness, confusion, loss of appetite, and nausea. The patient was diagnosed with new onset diabetes presenting with DKA, hyperglycemia, and acute kidney injury. Glucose 520 mg/dL on serum chemistry, bicarb 17, and anion gap 2.*				
BP 114/74 HR 102 T 37.3 R 20 SpO_2 94%	Glucose greater than 250 mg/dL Dry mouth, dry skin Polyuria, polydipsia, polyphagia Changes in mentation Kussmaul respirations	Diabetes type 1 Diabetes type 2 Long-term steroid use Non-compliance with insulin therapy Infection Trauma	Urinalysis and culture Serum ketones Arterial blood gas Blood culture CBC and chemistry Cardiac monitoring Neuro assessments Critical care Insulin therapy, hydration, electrolyte replacement	Fluid volume status Increased risk for infection Knowledge deficit regarding glucose management
Addisonian crisis [121, 122]. *A 67-year-old undergoing treatment for recurrent metastatic uterine leiomyosarcoma. She presented with fatigue and altered mental status. The patient was diagnosed with adrenal insufficiency secondary to hypophysitis following immunotherapy.*				
BP 78/54 HR 116 T 36.2 R 22 SpO_2 96%	Tachycardia Altered mental status Dry skin Hypotension Low fasting blood glucose	Addison's disease Prolonged administration of glucocorticoids Infection Cancer Stress ACTH deficiency Hypopituitarism Hypothalamic-pituitary disease	Serum cortisol level Chemistries High-dose IV corticosteroid therapy Cardiac monitoring ACTH stimulation test (cosyntropin)	Fluid and electrolyte management Fall precautions

Table 6.7 (continued)

Vital signs	Signs and symptoms	Risk factors/ contributing factors	Potential tests/ interventions	Nursing considerations
Hypophysitis [119, 123, 124]. *A 57-year-old male with recurrent metastasis renal cell carcinoma s/p radical left nephrectomy and right femur radiation 2 years ago. Current therapy includes nicolumab and ipilimumab. Complicated with immunotherapy related hypophysitis and hypothyroidism requiring high-dose steroids, now being tapered down. He presented with new onset dizziness.*				
BP 104/68 HR 126 T 37.2 R 20 SpO_2 95%	Fatigue Headache Dizziness Nausea/vomiting Altered mental status Visual disturbances Fever	Immunotherapy with ipilimumab Hormone imbalances	ACTH Thyroid panel	Gastric ulcer prevention High risk for infection
Thyroid storm [125–129]**.** *A 59-year-old male with papillary carcinoma with metastatic disease to the cerebellum, cervical nodes, thoracic nodes, lungs, bones, and spine. The patient presented with tachycardia. The patient was diagnosed with thyrotoxicosis with atrial fibrillation.*				
BP 147/92 HR 120 T 37.6 R 22 SpO_2 97%	Tachycardia Anxiety Diaphoresis Atrial fibrillation Tremors	Type 1diabetes Thyroid cancer TSH-secreting pituitary adenoma Adrenal insufficiency Untreated hyperthyroidism	Thyroid panel Antithyroid medication Cardiac monitoring	Monitor cardiac status, at risk for decreased cardiac output
Acute ischemic stroke [130–135]. *A 73-year-old female with low-grade follicular lymphoma, atrial fibrillation who presented with tremors and altered mental status. Patient family stated approximately 1 hour ago, the patient started complaining of a headache and mentation began to deteriorate. The patient's daughter stated they brought her in when "she was not making sense when she was talking."*				
BP 166/82 HR 76 T 37.1 R 20 SpO_2 94%	Altered mental status Sudden headache Numbness Ataxia Dysphasia	Hypertension Diabetes Malignant tumor Atrial fibrillation	Stroke protocol Verify platelet statements	Ensure patient is eligible for tPA prior to initiation
Acute myocardial infarction [136–140]. *A 51-year-old male cancer patient. Current suspicion of cancer. The patient recently (2 days prior) had a lymph node biopsy of cervical nodules; biopsy results pending. The patient reporting to the ED with chest and back pain.*				
BP 160/98 HR 46 T 36.7 R 22 SpO_2 92%	Chest pain/pressure Dyspnea Diaphoresis	Hypertension, cardiac and pulmonary disease Diabetes Cardiotoxic medications Hypertension Hyperlipidemia	EKG CBC and chemistry Troponin trends Interventional radiology	Acute pain management Tissue perfusion Activity intolerance Risk for excess fluid volume
Pancytopenia [103, 141–144]. *A 42-year-old male with a recent diagnosis of AML and recent induction chemotherapy treatment. Presents with shortness of breath, gingival and rectal bleeding.*				
BP 90/60 HR 116 T 37.2 R 20 SpO_2 96%	Shortness of breath Pallor Fatigue Bleeding Tachycardia	Hematologic cancers Hepatitis Chemotherapy Recent chemotherapy Sepsis Malignancy	CBC with diff ABORh Blood product replacement	Risk for infection Shortness of breath caused by anemia exacerbation with activity Risk for bleeding, high-risk for fall with injury Replace lowest blood product first to prevent deterioration related to pancytopenia

COVID 19: An Enhanced Threat to Cancer Patients

It is believed that patients with comorbid conditions, if infected, are at a heightened risk of manifesting complications associated with the virus [153]. Patients with cancer therefore remain at the forefront of this concern. Based on a recent Chinese cohort, patients with cancer had an increased risk of suffering severe events (intensive care unit admission, assisted ventilation or death) compared to those without cancer (39% vs. 8%, p = 0·0003) [154]. The threat the virus poses to medically compromised and noncompromised populations has therefore prompted extensive operational safety measures.

Table 6.8 Case study: end of life in advanced-stage cancer

Vital signs	Signs and symptoms	Risk factors/ contributing factors	Potential tests/ interventions	Nursing considerations
Triple threat [145–147]. *An 89-year-old male with stage 4 lung cancer on a clinical trial treatment regimen presents to triage with shortness of breath, altered mental status, and increased lethargy over the last couple of days. The patient presents with his adult son who is his primary caregiver and provides the history. He has visited the ED 3 times in the last 2 weeks for similar chief complaints resulting in admission to the hospital.*				
BP 101/56 HR 113 T 37.2 R 24 SpO_2 92% (on 3 liters/min via nasal cannula)	Delirium, altered mental status, or confusion in the last week Shortness of breath or difficulty breathing at rest or on minor exertion, such as toileting Spending more than 50% of their time in bed, or poor performance status with decreasing independence	Advanced stage cancer "Triple threat" symptoms at triage presentation Clinical trial, potentially indicating "Hail Mary" attempt to cure cancer Multiple ED visits may increase in the last weeks of life Patient may be nearing end of life Does the patient have advance care planning documents in place?	Discuss goals of care early in the encounter to prevent unwanted ICU admissions or invasive procedures Establish code status and provide realistic expectations of care to patient and family Ensure holistic approach and provide all necessary parties to produce a positive outcome	Provide support to patients and families to the best of your ability Use available resources to help provide patients/families with information. It takes a whole team to successfully have "goals of care" conversation in the ED You do not need to have all the answers as an ED nurse. Consult the experts in their specific areas (chaplaincy, social work, case management, palliative medicine, hospice, etc.) to assist in planning for those specific needs Ensure advance care planning documentation is available for all to see in the medical record to minimize confusion in an acute event regarding what the patient's wishes truly are Ensure the patient is comfortable – just because you are not providing curative treatment for the cancer does not mean they shouldn't receive treatment for infections, reversible conditions, and symptom management

Preventing Cancer Patients from COVID-19 Exposure from ED to Disposition

Notably, public safety measures in place are designed to reduce preventable hospital admissions and elective procedures [155]. These measures do not fully serve the interests of patients with cancer, who require continuous care inclusive of, but not limited to, diagnostic tests and therapeutic interventions. In this sense, both limitations in medical care and potential COVID-19 exposure could be risky, or even fatal [156].

It is for these reasons that remarkable efforts are taken by hospital personnel to screen for exposure to COVID 19 at hospital entry points. The oncologic ED is a main entry point for patients with cancer and as such, it adheres to the guidelines and recommendations put forth by the Center for Disease and Control (CDC) [157]. We share our adapted screening and preventative measures below.

Screening for COVID-19 and Safety Measures

- Staff member(s) are stationed near all ED and facility entrances (outdoors if weather and facility layout permit), or in the waiting room area, to ensure patients are screened for symptoms and fever before entering the treatment floor.
- Patients are provided with a face mask upon ED entry.
- Patients are screened for fever or symptoms consistent with COVID-19.
- Patients are directed to designated waiting areas which are divided to separate symptomatic from asymptomatic.
- Patients are separated by at least 6 feet; the area for symptomatic patients is at least 6 feet away from the area for patients without symptoms.
- For patients in need of urgent care, ED providers are notified immediately.
- Alerts and signs are posted in strategic places around the ED and the facility at large, with instructions for patients with fever or symptoms of respiratory infection.

Considerations for ED Staff

- Staff members in charge of screening patients remain 6 feet away from the patient until he or she is determined to be symptom-free and afebrile (temperature is determined by active temperature monitoring).

- Screening staff wear facemasks and shields (for source control) but do not need to wear PPE if they are separated from patients by a physical barrier such as glass or plastic window.
- Screening staff ensures these interactions as brief as possible by limiting the interaction to screening questions only.
- For staff members who must be within 6 feet of a patient, they are required to wear appropriate PPE, including an N95 or higher level respirator, gloves, and eye protection.

Post Patient Screening and Treatment Room Assignment

- Notification of direct patient care staff of the presence of a symptomatic patient.
- Safe and prompt transfer of symptomatic patients from triage to treatment rooms.
- Posting of appropriate isolation signs outside treatment rooms to communicate status.
- Immediate disinfection of waiting areas occupied by symptomatic/exposed patients and surfaces that were within 6 feet of the symptomatic patient; this is in addition to the regular (frequent) baseline cleaning and disinfection process that occurs for the entire waiting area.
- Items that cannot be disinfected remain with the patient or discarded.

Regulatory Standards for Oncologic Emergency Departments: Brief Introduction

Healthcare organizations that achieve accreditation through a Det Norske Veritas (DNV) or The Joint Commission (TJC) "deemed status" survey are determined to meet Medicare and Medicaid requirements and may receive payment from the Center for Medicare and Medicaid Services (CMS). Accreditation does not protect a hospital from an additional CMS survey. All healthcare organizations are still subject to a CMS survey based on a complaint or a validation survey [158]. Validation surveys usually occur within 60 days of the accreditation survey; however, TJC, in collaboration with CMS, has been working on redesigning the validation survey process. The objective of the redesign is to eliminate the validation survey and for CMS to oversee the accreditation process; thus, both may survey an organization at the same time [159].

CMS developed comprehensive Conditions of Participation (CoPs) and Condition for Coverage (CfC) that hospitals and other healthcare entities must meet to initiate or continue their participation in the Medicare and Medicaid programs [158]. All hospitals, including acute care, critical access, long-term care, children's, psychiatric, and cancer hospitals, are included. There are various key conditions of participation chapters for hospitals, and they all involve Emergency Services to varying degrees. Table 6.9 lists CMS subpart chapters applicable to an emergency setting but is not all-inclusive list of the regulatory standards [158].

Emergency services, one of the optional services that may be reviewed by CMS, are often an integral part of most hospital surveys. Thus, any organization with an ED will need to adhere to these standards. Table 6.10 displays additional subchapters that each hospital must examine to ensure compliance although some areas may not apply [158].

An emergency preparedness plan is required by all healthcare facilities. These guidelines will ensure compliance and demand a proactive approach to adequately plan for natural and man-made disasters. The CMS State Operations Manual, Appendix Z, Emergency Preparedness will guide the development of a comprehensive plan and will likely involve collaboration between the ED and the organization to meet the expectations or standards [160].

CMS is the single largest payer for healthcare in the United States, and the CoP health and safety standards are the foundation or *minimum* standards for its beneficiaries. There are other federal laws that all oncologic urgent or EDs or centers must follow. They include but are not limited to the Emergency Medical Treatment and Labor Act (EMTALA), originally part of the Consolidated Omnibus Budget Reconciliation Act (COBRA) passed in 1986 to address anti-dumping issues. Although motivated by the highly publicized anti-dumping incidents, EMTALA was intended to prevent inadequate care and delay or denial of

Table 6.9 Center for Medicare & Medicaid Services subpart chapters

482.11 Administration	482.25 Pharmaceutical services
482.12 Governing body	482.26 Radiologic services
482.13 Patients' rights	482.27 Laboratory services
482.15 Emergency preparedness	482.28 Food and dietetic services
482.21 Quality assessment and performance improvement program	482.30 Utilization review
482.22 Medical staff	482.41 Physical environment
482.23 Nursing services	482.42 Infection control
482.24 Medical record services	482.43 Discharge planning
	482.45 Organ, tissue & eye procurement

Table 6.10 Center for Medicare & Medicaid Services optional hospital services chapters

482.51 Surgical services	482.56 Rehabilitation services
482.52 Anesthesia services	482.57 Respiratory care services
482.53 Nuclear medicine services	482.54 Outpatient services
482.55 Emergency services	

Table 6.11 Reporting violations of the Emergency Medical Treatment and Labor Act (EMTALA)

EMTALA violations are reported to:	Purpose
Office of Inspector General (OIG)	To issue and enforce civil monetary penalties
Office of Civil Rights	To evaluate if there are any civil rights violations
Justice Department	To evaluate for Hill-Burton Act violations
Internal Revenue Service	To evaluate of tax-exempt status
Joint Commission or Det Norske Veritas (DNV)	To review accreditation status, patterns and trends

treatment of an emergent condition for the uninsured person to include pregnant women seeking medical advice. EMTALA is a federally mandated social policy calling for access to healthcare that hospitals and physicians must address [160, 161]. EMTALA violations are also reported to other regulatory entities listed in Table 6.11. Of note, the most common violation is an inappropriate Medical Screening Examination [161].

The CMS State Operations Manual interpretive guidelines Appendix V is devoted to Emergency Services and EMTALA and provides direction with the EMTALA demands [162]. CMS is responsible for all investigations of EMTALA violations and is partially responsible for enforcements through citations, often designated as "Notice of Termination from Medicare," which gives a hospital 23 days to come into compliance. A plan of correction will need to be submitted with credible evidence of compliance beyond the date of reinspection. On day 19, a notice of termination is published in local newspapers, unless a plan has been submitted, accepted, and re-survey shows compliance within the 23 days [163].

Possible EMTALA violations need to be reported by the receiving hospital within 72 hours, and healthcare organizations have significant sanctions for failure to report, to include termination from Medicare participation. Some states require any healthcare employee with knowledge of a violation to report timely. CMS expects organizations to self-report violations. However, organizational practices vary. Blatant violations may go uncited, while minor or even marginal incongruities may receive punitive enforcement. Often, this variability is related to the interpretation of the law. The Government Accounting Office has reported the variability to Congress, calling for improved consistency. Currently, the inconsistencies continue [162].

Any EMTALA or CMS investigation or validation survey is very demanding for most hospitals. Every detail of hospital operation is often under intense scrutiny. The evaluation of compliance is very black and white, and there is no gray. Either you are compliant, or you are not. Also note, there are no pre-termination appeal rights under EMTALA [158].

COP investigations often lead to "lengthy citations for every dirt mark or dust covering found on any location in the facility. Inspectors are reported to literally surveyed facilities using magnifying glasses and flashlights" [163]. Oncologic hospital administration or nurse leaders do not expect CMS or EMTALA surveys to be as concrete as they are known to be and may struggle significantly. Even minutes are reviewed in detail. There is no gray, only black and white, when determining compliance during a CMS survey. Again, either you are compliant, or you are not [163].

There are two types of citations that CMS can issue. The "condition-level" is considered more serious and indicates that a hospital is not in substantial compliance. A "standard-level" deficiency is cited when a hospital is out of compliance with one aspect of the regulations and it is considered less severe than the condition-level citation. Most surveys have a mix of both types once the final report is released. The hospital has only 10 days to submit a correction plan once they receive the Form CMS-2567 report. If the plan of correction is not accepted as written, the hospital is asked to submit a revised plan [158].

When surveyors determine that the hospital's noncompliance from regulatory standards constitutes an immediate threat to patients' health and safety, they will issue an "Immediate Jeopardy" (IJ) [164]. An IJ determination forces a hospital to immediately stop and correct the underlying problems and is considered the most serious type of violation. Once a hospital or healthcare organization receives an IJ citation, it is given a short time frame to fix the deficiency. If the organization fails to address the IJ as CMS demands, CMS will terminate the facility's Medicare and Medicaid funding. Losing accreditation has a significant impact and can be devastating since the government is the largest payer, and loss of accreditation will affect hospital insurance rates, among other things. It may erode a hospital's infrastructure quickly; physicians stop sending patients, the staff starts leaving, and an organization quickly spirals downward [164].

Over the last few years, there have been several oncologic hospitals that have been surveyed by CMS. The plans of correction are considered public knowledge and are available for review online. They are an excellent source of information to strengthen your organization. Hospitals grow significantly after a survey, becoming stronger and more focused.

Interdisciplinary Collaboration

An essential aspect of providing high-quality care to cancer patients in the ED is the interdisciplinary team's collaboration and cohesion. As displayed in the case studies in this chapter, the cancer patient requires many different needs when presenting to the ED and will encounter many different teams. The collective plan must be centralized around the

patient and family and closed-loop communication is vital to preventing errors and for the administration of appropriate treatment.

The cancer patient population's needs require multidisciplinary care to address all aspects and provide holistic and comprehensive care. Communication between teams is essential for preventing errors and identifying issues in the plan of care. High-reliability organizations promote a just culture environment, seeking to improve systems and prevent human error. This means facilitating an environment where every healthcare team member feels supported to identify patient safety issues and speak up when advocating for the patient and family [164].

Recommendations to promote interdisciplinary collaboration include discussions from all stakeholders with practice changes and an opportunity to provide input, professional practice recognition from interdisciplinary members, and establish clear policies and procedures that clearly and concisely delineate role responsibilities. Another great tool for enhancing teamwork is interdisciplinary high-fidelity simulation exercises [165]. This can reveal strengths and opportunities for improvement without patient safety being jeopardized.

This textbook is an excellent example of interdisciplinary collaboration in action. The information can help physicians work more effectively with their nursing partners by providing information relevant to their scope of practice and how it applies to oncologic emergencies while adhering to the regulatory requirements. As the field of oncologic emergencies continues to evolve, the integration of multidisciplinary teams must continue to develop cohesively to create a useful model for patient-centered care.

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Palliative Social Work

7

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Introduction

Cancer patients may require emergency department (ED) care as a result of symptoms or complications of the disease itself, from the side effects of cancer treatment, including chemotherapy or radiation therapy, or from intercurrent injury or illness unrelated to cancer. Sepsis, pain, neutropenia, fever, deep vein thrombosis, nausea/vomiting, and failure to thrive are common symptoms that prompt oncologic emergency care [1–3]. Despite the overall decrease in cancer death rates, ED visits for cancer-related emergencies are on the rise [4]. One Australian study showed that while the number of deaths in the ED for cancer and non-cancer-related presentations was similar, the number of inpatient deaths for patients with cancer was significantly higher than for non-cancer patients [5]. The impact of a new cancer diagnosis, worsening prognosis, or transition to end-of-life care exacts physical, emotional, financial, and psychosocial distress on patients and families. Medical social workers are key interdisciplinary team members within the inpatient, outpatient, and home care settings who intervene along the continuum of illness. They are specifically trained to assess the patient's adjustment to illness and treatment, as well as any social and financial concerns that may impact medical decision-making. Social workers also provide therapeutic interventions to enhance patient coping, reduce caregiver distress, and ensure continuity of care across settings [6].

When patients with oncologic emergencies and their families present to the ED, social workers may be called upon to intervene with issues involving the entire spectrum of cancer, from a new diagnosis to end-of-life care. In both inpatient and outpatient settings, oncologic social workers are trained to provide a variety of interventions to assist patients and families coping with cancer, including assessment of psychosocial needs, adjustment to illness and side effects of treatment, and linkage to community resources. Palliative social workers may also intervene to assist oncologic patients in crisis where primary attention may be placed on pain and symptom management, goals of care conversations, advance care planning, or education and counseling regarding end-of-life care. This chapter examines social work's involvement with oncologic patients in the ED, as well as the oncologic social work role in the outpatient setting, and suggests potential partnerships and collaboration among ED, oncologic, and palliative social work.

The Role of the ED Social Worker

The role of the ED social worker varies greatly, given the diversity of the patient population and the emergent nature of many social work referrals in this setting. ED social work consults are imperative for trauma victims and their families, victims of assault, homeless individuals, persons with substance use disorders, and minors [7]. Due to the time-intensive nature of these referrals, it may be difficult for the ED social worker to consult on less urgent referrals, including patients who, after a diagnostic evaluation, confront a newly diagnosed cancer. Despite these constraints, ED social workers may be the first psychosocial clinicians to see patients with life-limiting illnesses who present with distressing symptoms or who may be actively dying [8].

ED social workers strive to maintain a careful balance by blending their responsibility to provide concrete services such as community resource referrals, medical equipment/home health setup, and placement in short-term or long-term care facilities, with therapeutic interventions, including crisis intervention. ED social workers also conduct psychosocial assessments and provide bereavement counseling when deaths occur in the ED [9]. A 2016 study in a large, urban trauma ED identified that the most common ED social work

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services provided were mental health services, followed by care coordination and then community resource information/referral [7].

Crisis Intervention

For ED social workers, priority referrals that require immediate intervention include domestic violence and sexual assault and elder or child abuse and neglect. In addition to providing support and crisis intervention, these referrals may also require consultation with law enforcement or state agencies as well as hospital security, as well as locating and supporting family members or friends, and maintaining constant communication with the ED physician and nurse. Given the sensitive and complicated nature of this work, the ED social worker may spend a great deal of time on such consultations. Crisis intervention skills utilized with victims of sexual assault and domestic violence include re-establishing coping skills, problem-solving to identify next steps, assessment for suicidality, provision of emotional support, and the resolution of concrete needs such as safety, housing, and financial support.

For patients who present with symptoms of depression, anxiety, suicidal ideation, or alcohol and drug abuse, but do not require inpatient admission, the ED social worker typically completes an assessment and provides brief counseling as well as linkage to community resources to ensure follow-up support. ED social workers with strong backgrounds in mental health may identify appropriate referrals to psychiatry or outpatient mental health agencies and provide brief interventions and education to interdisciplinary team members on strategies to help patients in this setting.

Complex Case Management

When a patient's ability to care for himself or herself is diminished but admission is not required, the ED social worker may be responsible for obtaining support through home-based health services. They also assist with applying for financial assistance to facilitate admission to a skilled nursing facility, as well as coordinating a plan for family and friends to support caregiving at home. For patients who need additional services, preventing a "social admission" by facilitating a safe discharge from the ED is important.

A Canadian study found that the ED social workers commonly assisted patients with financial concerns and discharge planning needs as well as adjusting to their illness and addiction [10]. Effective discharge planning reduces unnecessary hospital admissions and coordinates the outpatient services a patient needs to allow them to safely remain in their home environment. The expertise and range of skills implicit in crisis intervention, mental health assessment, and complex case management are essential to the care of oncologic patients and their families who present to the ED for help.

ED Social Work Role with Oncologic Patients

When oncologic patients present to the ED with complications from their disease or treatment, the ED social worker may be asked to see patients with concomitant symptoms of depression, anxiety, or suicidal ideation, while also evaluating caregivers who may be exhausted from providing care. Newly diagnosed cancer patients, as well as cancer patients who come to the ED in lieu of a visit with their primary physician or oncologist, may be referred to the ED social worker for assistance with medical follow-up, evaluation, and treatment, as well as provision of concrete services such as home health care or medical equipment.

When oncologic patients present to the ED at the end of life, the ED social worker provides emotional support to the patient and family, communicates with the hospital chaplain as requested by the family, and helps identify a private space for family members to gather and grieve. While there is no published research delineating the role of ED social work with oncologic patients, many of the skills outlined above are integral to assisting oncologic patients and their families.

Psychosocial Issues for Cancer Patients in the ED

Diagnosis of Cancer in the ED

A new diagnosis of cancer may elicit strong emotions and can induce a great deal of stress and anxiety for patients and families. It may cause the patient to experience feelings of loneliness, abandonment, and loss of control over their situation [11]. The ED social worker may be called upon to provide emotional support while identifying and clarifying, in consultation with the emergency physician, any real or perceived fears surrounding a new diagnosis, prognosis, or treatment. Providing patients and families with the necessary time to integrate a new diagnosis is essential to allowing them to consider decisions about appropriate treatment and continuing medical care [11]. For patients who decline further evaluation and treatment, it is essential that the patients understand the potential consequences of avoiding further care. An ED social work assessment of concerns and fears following a new diagnosis of cancer may provide the patient with an alternative plan of care aside from hospitalization,

such as follow-up with an oncologist to review and integrate medical options. Below is a case study of a newly diagnosed cancer patient in the ED that demonstrates the ED social worker's role with patients/families and the interdisciplinary team.

Case Discussion 1

Emergency Department Social Worker

The ED social worker receives a call from an emergency physician to see a 63-year-old Latina woman, who, with her three adult children, is anxiously awaiting the results of a CT scan of her pelvis and abdomen. Prior to this ED visit, her medical history includes diabetes and asthma. She presents with rectal bleeding, severe abdominal pain, and dizziness. The emergency physician informs the ED social worker that the patient has a new diagnosis of metastatic anal cancer and that he would like the social worker to assist as he provides this information to the patient and her family. The patient has no primary care physician and must be admitted to the hospital for further evaluation and consideration of treatment options.

The ED social worker had spoken with the patient earlier in the day while the patient was waiting. The patient confided, "I bleed every time I'm on the toilet, for the last few months." When the social worker inquires if she had told anyone, the patient states that she did not want to tell her family because she was scared. As the social worker begins to explore the patient's fears about telling family, the patient begins crying and pulls out rosary beads from her pocket. The patient explains that her youngest daughter is getting married in a few months and that the focus should be on the young, not the old. She goes on to say she has led a full and happy life and that it is up to God to decide her fate.

With the patient's permission, the ED social worker contacts the Catholic chaplain on call for the ED to be present at the family meeting. The ED social worker secures a private space for the patient and family to meet so that they can process this new diagnosis in a quiet setting. As the emergency physician explains the results of the tests done in the ED and describes the patient's diagnosis, prognosis, and treatment options, the patient and her children begin to cry. While the social worker and the chaplain comfort the patient/family, the emergency physician sits quietly, in order to allow them time to process this information.

After a few minutes, the emergency physician confirms with the patient that she has heard the words and is beginning to integrate the significance of her medical condition and the treatment options. Following this discussion, the ED social worker acknowledges the unique emotional responses of the patient and family and describes the oncologic and/or palliative services that can be provided concurrently with the chemotherapy or radiation that the patient may receive while in the hospital. The emergency physician concurs with the ED social worker, describing how the patient may benefit from specialized symptom management and the provision of psychosocial and spiritual services for both the patient and family. The patient is admitted to the hospital late that evening and is seen by oncologic and palliative consultants the next day. The ED social worker ensures a seamless transition by communicating with the inpatient unit social worker.

Communication in the ED

Due to an often chaotic and busy environment, ED clinicians are often unable to spend significant periods of time with patients/families. As most patients arrive to the ED in crisis and distress, it may be difficult for them to comprehend a complete picture of their medical problem and proposed treatment. The medical jargon and complex terms used by healthcare professionals may represent a foreign language to patients/families, regardless of their educational level. ED social workers can assess the patient's/family's health literacy and understanding of medical information and then work with the physician to clarify that the patient understands the care they are receiving. The essential role that social workers play as part of the healthcare system is evidenced by their frequent initiation, implementation, and support of end-of-life discussions with patients, families, and other caregivers [12]. Furthermore, social workers advocate on behalf of patients to physicians and nurses, increasing awareness of psychosocial issues along the continuum of illness and the benefits of early referrals to palliative care or hospice.

In addition to normalizing the challenge of integrating information when in crisis, the care taken to help patients and families to anticipate the next steps in resolving their medical crisis models a relationship that highlights both the emotional and informational needs of patients and families. Despite the often limited time that is spent with a patient, all clinicians who care for seriously ill patients contribute to the meaning making and processing of coping with illness. While ED interactions may be brief, they can forever impact patients and families.

ED as Primary Healthcare Site

Patients who typically use the ED as their primary healthcare site are more likely to learn of their cancer diagnosis in the ED. The fragmentary nature of emergency care may limit the possibility of establishing continuity of care and a predictable relationship with a provider after diagnosis [13]. For

patients with advanced cancer who present to the emergency department, one British study found that anxiety related to the disease related to patient interpretation of symptoms, feelings of comfort and safety within the hospital environment, difficulties accessing community healthcare services especially after hours or for urgent reasons, and previous patterns of health-seeking behavior are the major drivers of seeking care in this setting [14].

For those individuals without insurance, social work involvement can be pivotal to helping patients organize their medical care and access available financial assistance, without which, treatment for their disease can be delayed and suboptimal. In working with patients/families to identify alternative care plans, as well as available community resources to assist with integrating a new diagnosis, the ED social worker serves as the link between the community, primary care, and hospital settings.

Language/Cultural Barriers

In one Michigan study, those diagnosed with cancer in the ED were found to come from lower socioeconomic backgrounds, were older, and more often disabled [13]. A large number of these patients were found to be dually eligible for Medicaid and Medicare up to 12 months prior to diagnosis compared to those diagnosed with cancer in other settings. Racial differences were also found in this study, with African Americans being significantly more likely to receive a cancer diagnosis in the ED [13].

A small study of Spanish-speaking patients in New York City found that they were frustrated both due to their inability to comprehend their prognosis, as well as difficulty in accurately expressing to clinicians their feelings surrounding cancer diagnosis and prognosis [15]. Advocating for the use of an interpreter for patients/families whose first language is not English can enhance understanding of medical information and minimize the emotional distress and confusion that emanates from such misunderstandings. An ED social worker's assessment of specific cultural concerns related to hospitalization, caregiving, and in some cases, receipt of medical treatment, allows the ED team to practice more culturally sensitive care.

A key tenet of social work practice is cultural competence or the ability to work in the context of cultural differences. Health disparities in ED pain management have been demonstrated, with one study showing that Hispanics were twice as likely not to receive pain medication for bone fractures as compared to non-Hispanic whites [16]. ED social workers can take the lead role in educating their interdisciplinary team members about these and other disparities as well as specific cultural concerns and traditions that may impact medical decision-making.

Caregiver Distress

Whether driven by distressing symptoms that are unmanageable at home, exhaustion from the intensity and/or longevity of caring for a cancer patient, or feeling overwhelmed by the responsibilities of caregiving, caregiver distress may be the root cause of an ED visit. ED social workers who screen for caregiver distress can work to determine additional sources of support in the caregiver's life and ensure a link to these services. A case example of an oncologic social work intervention for a distressed caregiver is provided at the end of this chapter.

The Role of the Outpatient Oncologic Social Worker

In addition to the acute medical needs that prompt ED visits and invite the interventions of ED social workers, oncologic social workers serve to address the unique psychosocial stressors that accompany a cancer diagnosis. These may include adjustment to a new cancer diagnosis, alterations in role and identity, changes in caregiver needs and family roles, impact on work and finances, and goals of care planning. For cancer patients, these transitions can be markers of ambiguous loss, or the unclear, indeterminate losses that are less acknowledged than death, but can greatly impact coping, sense of control, and psychosocial functioning in both the patient and family [17, 18]. These losses can also trigger feelings of anticipatory bereavement, in which patients and families begin the process of mourning, coping with loss, and psychosocial reorganization in preparation for death. This process can trigger mixed emotions such as helplessness, denial, confusion, and guilt but, if managed effectively, may provide patients and their families with improved communication and meaningful interactions at the end of life [19].

Prior to a cancer diagnosis, patients may not have had needs that would necessitate an interaction with a social worker. The oncologic social worker may be their first introduction to such services. Once this connection is made, the oncologic social worker can link patients and their families to concrete resources in the community, as well as provide therapeutic interventions to address psychosocial needs. The oncologic social worker becomes the conduit of communication, linking the work done in the ED with the work of the outpatient oncologic team; thus avoiding a "new beginning" for patients and families and supporting continuity of care in the process. It is the author's experience that oncologic and ED social workers typically collaborate and communicate to ensure smooth transitions for patients in need between specialties and across outpatient and inpatient settings.

Social workers are the primary psychosocial professionals available to patients receiving medical treatment [20, 21].

While medical social workers have become more broadly available in healthcare settings, oncologic social workers have evolved as a subspecialty within the field [22]. The psychosocial needs of patients with cancer have become increasingly complex as treatment has shifted to the outpatient setting. The broader range of treatment options available to patients has complicated decision-making and increased both patients' and families' care management responsibilities [23–25].

Traditional social work interventions in outpatient oncologic settings include biopsychosocial assessments, psychoeducation, counseling, linking patients to community resources and coordinating the provision of concrete services including home care, hospice, durable medical equipment, and transportation. Social workers are highly skilled practitioners who are trained to provide screening, assessment, and therapeutic interventions across the cancer continuum including primary prevention, diagnosis, treatment, survivorship, palliative care, end of life, and bereavement [22]. Oncologic social workers are knowledgeable about cancer and its treatments as well as psychosocial aspects of illness, cultural and spiritual influences, pain and symptom management, finances, community resources, and research in the field of psycho-oncologic [22, 26].

Clinical Interventions

Oncologic social workers spend considerable time with patients and/or family members discussing their adjustment to a cancer diagnosis. Individual counseling can help the patient determine specific concerns and set priorities [26, 27]. The focus of clinical work in health care is on enhancement of coping rather than psychopathology [28]. The goals of clinical interventions are to reduce anxiety and assist in clarifying misconceptions and correct misinformation, as well as decrease feelings of isolation [22, 29]. Researchers have shown that psychological interventions can improve the emotional and physical health outcomes in patients with cancer [29, 30].

Cognitive Behavioral Interventions

Cognitive behavioral therapy (CBT) combines cognitive psychotherapy with behavioral interventions. It seeks to reduce emotional distress by identifying, challenging, and eliminating irrational beliefs, and encouraging patients to change their maladaptive preconceptions and behaviors [31, 32]. These techniques may include hypnosis, guided imagery, progressive muscle relaxation, and biofeedback, which are utilized during individual or group sessions [26, 29]. Social workers frequently obtain specialized training for this type of work [26]. Used either alone or in conjunction with medication, behavioral methods are effective for treating side effects associated with cancer. These include anticipatory nausea and vomiting associated with treatment, heightened anxiety, and pain [33, 34].

Relaxation Techniques

Relaxation techniques guide patients to achieve control over their muscles and thoughts, in order to reduce emotional distress [31]. Progressive muscle relaxation involves systematic tensing and relaxing of various body parts. The practitioner describes comfortable sensations in muscle groups usually progressing from head down to feet or from feet up to head. Patients are encouraged to practice these techniques at home to enhance competence and achieve mastery [31]. Visualization of restful scenes associated with pleasurable thoughts is another technique used to promote a sense of relaxation and calmness, allowing patients to feel more in control of their feelings. Social workers practicing these techniques should obtain specific training in these areas [26]. The growing use of complementary therapies (such as meditation, relaxation, hypnosis, and visualization) has resulted in their increasing availability in hospitals and oncologic centers [35–37].

Supportive Counseling

Counseling helps patients and their families manage the multiple problems associated with chronic illness [26]. Individual supportive counseling can decrease the distress and disruption experienced with a cancer diagnosis. While there is no clear definition for supportive psychotherapy, this approach is generally considered an intervention that can be used intermittently or continuously. This patient-centered flexible approach assists patients in dealing with distressing emotions by reinforcing strengths [31, 38]. Supportive counseling emphasizes the importance of compassion, empathy, and support in working with patients [29]. An important goal of counseling in oncologic social work is to help the patient and/or family maintain or redefine hope [26], moving beyond equating hope with cure to broader meanings, values, and intentions that are beyond the limits of an illness.

Crisis Intervention

A significant crisis can be triggered with the initial cancer diagnosis, throughout the course of treatment, when the disease recurs, and at the termination of curative therapy. Therefore, oncologic social workers may use crisis intervention techniques on a recurring basis throughout the illness trajectory. Oncologic social workers help the patient and family explore and clarify feelings, understand how to manage these

feelings, and teach new ways of coping, including solving problems [34, 39]. The oncologic social worker encourages familiar coping mechanisms, while also providing resources and support to patients experiencing a loss of stability [39].

Psychoeducation

Providing education to cancer patients serves to reduce the sense of helplessness that results from uncertainty and lack of knowledge. Psychoeducation can provide patients with a sense of mastery over their illness. It can involve disease-specific information and may also include information about coping, side effects, and wellness [29]. The goal of this intervention is to enhance coping skills and empower patients to become active participants in their care [29]. The information provided should be tailored to meet the patient's expectations, preferences, diagnosis, treatment, and prognosis. Information can also be related to maintenance of maximal health, coping, and financial/legal concerns.

A patient's educational needs change over time, such as during and after treatment [40]. A patient's primary language and reading comprehension level are also important factors for social workers to consider when adapting psychoeducational materials to cancer patients and their families. Oncologic social workers often provide patients with brochures, booklets, and materials from well-known sources, such as the Leukemia and Lymphoma Society, CancerCare, and the American Cancer Society, or refer patients to resource libraries and/or trusted websites. An understanding of patient health literacy is essential to effectively use these resources. Table 7.1 lists national resources that provide support, information, and/or financial assistance to those with cancer and their families.

Table 7.1 Resources for general cancer support[a]

Resource	Website/phone
American Cancer Society American Psychosocial Oncologic Society	cancer.org 800-227-2345 www.apos-society.org 866-276-7443
cancer.net	cancer.net 888-651-3038
CanCare	CanCare.org 888-461-0028
CancerCare	cancercare.org 800-813-HOPE
Cancer Hope Network	CancerHopeNetwork.org 800-552-4366
Cancer Financial Assistance Coalition	cancerFAC.org
Cancer Support Community/ Gilda's Club	CancerSupportCommunity.org 202-659-9709
Imerman Angels	Imermanangels.org 877-274-5529
Livestrong	Livestrong.org 855-220-7777
National Cancer Institute	Cancer.gov 800-4CANCER
National Comprehensive Cancer Network	nccn.org 215-690-0300

[a]This listing represents national organizations providing information to cancer patients. There are many more excellent disease-specific organizations and local organizations

Table 7.2 Description of psychosocial interventions that may be used with oncologic patients in the ED

Intervention	Description	Outcome
Cognitive behavioral therapy	Assists patients in identifying and changing maladaptive thinking and behaviors, in order to reduce negative emotions and facilitate psychological wellness	Reduces anxiety, increases problem-solving skills, increases understanding of maladaptive cognitions, and enhances coping
Relaxation techniques	Encompasses a variety of techniques to calm thoughts and muscles, in order to allow patients to feel more in control and at ease	Reduces anxiety, increases sense of control, enhances coping
Supportive counseling	Focuses on helping patients to cope with distressing emotions, reinforces pre-existing strengths, and promotes adaptive adjustment to illness	Enhances coping by establishing a therapeutic alliance, reduces anxiety
Crisis intervention	Time limited, used intermittently; focuses on symptom reduction; expression of feelings are encouraged and tangible support is provided	Reduces psychosocial symptoms, mobilizes social supports, increases sense of self-competency
Psychoeducation	Utilizes educational resources and provides information to reduce feelings of helplessness while increasing the patient's knowledge and sense of control	Prevents ED admissions (i.e., may increase compliance to medical recommendations), fosters improved decision-making, reduces anxiety, increases sense of control

Cancer patients may benefit from numerous intervention techniques and programs. Psychiatric interventions play a significant role in the comprehensive care of cancer patients. The list provided in Table 7.2 is not an exhaustive list of interventions but rather a compilation of interventions that are utilized by oncologic social workers in practice, which may also be applicable to oncologic patients in the ED.

Case Discussion 2

Oncologic Social Worker Interventions to Prevent an ED Visit

Charlotte was a 57-year-old African American female with metastatic triple-negative breast cancer. Charlotte was well

known to her outpatient oncologic social worker (OSW), who had been working with her since she was initially diagnosed with cancer a year before. The OSW assisted with referral to a home hospice program which had an inpatient unit affiliated with the cancer center. Several days later, the OSW received a call from her adult daughter, "Julie." She was upset because the hospice nurse told her that Charlotte was entering the dying stage and they were unwilling to transfer her to the inpatient unit. Julie had a 4-year-old daughter at home and had been explicit at enrollment that she did not want her mother to die at home. She was very frustrated that the hospice staff was not helping her to facilitate an inpatient admission as they believed her symptoms could be managed at home. Julie stated that she was going to call an ambulance to bring Charlotte to a hospital, if the hospice agency did not transfer her mother immediately. In order to avoid the crisis of an ED visit and added distress for Charlotte and her daughter, the OSW intervened and advocated for an immediate inpatient admission since Julie was going to call 911/ambulance if the agency did not act right away. The OSW also spoke to Julie and educated her about alternative options (other hospice programs with inpatient facilities), in order to avoid her calling 911/ambulance to have her mother brought to an ED. Within an hour, Charlotte was brought to the inpatient hospice unit. This case example demonstrates one way that continuity of relationship with an outpatient OSW, even in the setting of a hospice admission, assisted in preventing an ED visit/hospital admission and optimized the care of a dying patient, containing further risk of complicated bereavement for Julie and her 4-year-old child.

The Role of the Palliative Social Worker

Palliative social work developed as palliative care teams sought to increase patient and family-centered care for seriously ill patients and because of the need for the unique assessment and interventional skills provided by social workers. Building on the fields of hospice, oncologic, critical care, and other established areas of practice [41], early leaders in palliative social work helped identify specific competencies in palliative care, targeted psychosocial interventions, and areas of research [42]. Social workers are core interdisciplinary clinicians on palliative care teams whose multifaceted role includes education and counseling on one's adjustment to illness, with special attention to the multidimensional aspects of pain and other symptoms, including the impact of life-limiting illness on the patient's mood, goals, and relationships [43]. Palliative social workers also help facilitate patient/family decision-making regarding goals of care and advance care planning and provide therapeutic interventions to help reduce anxiety and distress in patients and families.

Palliative Social Work Initiative in the ED

As increasing numbers of ED's strive to integrate palliative care into their clinical setting with the goal of improving care for seriously ill patients and encouraging earlier palliative care consults and hospice referrals [44], there are opportunities for palliative social workers to provide consultation to patients, families, and clinicians in the ED. One study of ED utilization found that visits for palliative care, dehydration, and altered level of consciousness were higher during the final two-week period of life than during the last 6 months preceding death [45]. Palliative social workers may be called upon to consult in the ED to help patients and families integrate the meaning of the medical crises while attending to issues such as advance care planning, goals of care discussions and facilitating transitions in care.

The palliative social worker can obtain medical information, specify functional limitations in the patient, and complete symptom assessments [46], as well as discover the patient's narrative of the event that led them to the ED. The ability to ascertain unmet palliative care needs and communicate the benefits of a palliative consult or a hospice referral to the emergency physician encourages their initiation from the ED [47]. Early referral to palliative care in advanced cancer patients has shown to improve quality of life and does not appear to shorten survival [48]. The palliative social worker can be expected to communicate with the palliative care team regarding symptom management needs for seriously ill patients in the ED.

Visibility of the palliative care team is important in the eyes of emergency clinicians. The palliative social worker may become the "face" of palliative care by regularly consulting in the ED, through collaboration with the ED social worker to assist seriously ill patients, or by providing education on palliative care principles to ED clinicians. Whether helping to increase collaboration between emergency medicine and palliative care, identifying patients who are appropriate for palliative care consults and hospice referrals, or providing specific psychosocial interventions to patients in the ED [47], palliative social work can play a key role in assisting oncologic patients and families.

Goals of Care Conversations in the ED at End of Life

The ED is often where changes in the patient's illness trajectory are recognized, and new plans of care are established: thus identifying end-of-life patients who may be appropriate for a transition in care is appropriate in this setting. For oncologic patients who present to the ED and are actively dying, or for those whose prognosis is poor, facilitating goals of care discussions can help clarify options for ongoing disease-

modifying therapies. Within these discussions, it is important to understand the patient's or surrogate's wishes related to initiating, continuing, or foregoing potentially life-prolonging treatment (e.g., endotracheal intubation). With the assistance of the emergency physician, the palliative social worker can help guide goals of care conversation to enhance patient and family's understanding of diagnosis, prognosis, and treatment options at the end of life, including palliative care and hospice.

The nature of an oncologic patient's emergency may also invite a conversation about advance directives or MOLST/POLST to include decisions about resuscitation, treatment preferences, and goals of care [47]. Palliative social workers have the clinical skills and knowledge to work with the physician to obtain, interpret, and assist in completing these advance care-planning documents. ED social workers are also knowledgeable about advance care-planning documents as well as pertinent state laws that may pertain to this process.

Social Work Initiatives to Prevent ED Visits

Given the importance of ED social worker's role in care coordination, and other ED clinicians referral to them for assistance with illness adjustment [7], there is tremendous opportunity for them to be involved in improving care for cancer patients in the ED. Based on the acuity of cancer patients, initiatives will likely involve social workers who are most often responsible for making and following up on home care and hospice referrals. An initiative to assist in the prevention of ED visits requires screening, anticipatory guidance, and knowledge of resources. For example, caregivers experiencing distress and exhaustion might be connected to community resources that provide respite care. Below is a case example highlighting one such instance.

Case Discussion 3

OSW Connecting an Oncologic Patient's Caregiver to Community Resources

James is a 63-year-old, African American male with pancreatic cancer living in Tennessee. James's sister, Millie, his only caretaker, lives in New York City. When Millie found out about his diagnosis, she moved him to New York City, as he had no family in Tennessee. James sleeps on Millie's living room sofa and she assists him by coming to his medical appointments, chemotherapy appointments, making sure he eats properly, etc. *Millie met with the oncologic social worker (OSW) to discuss her feelings of being overwhelmed by the level of care that he required and she indicated that she felt she needed help. The OSW offered to make a home care referral and Millie agreed. After several weeks of home care, Millie reported that she was still feeling stressed and overwhelmed, and she requested that James be admitted to a nursing home. James has Medicaid, prompting the OSW to suggest that Millie try a day program at a nursing home close to where she lived. Millie agreed to the referral and James began attending the day program 4 days per week. The day program provided James with meals, activities, and transportation to and from Millie's apartment, all covered by his insurance. Millie was relieved by the referral, since the facility was one that she liked and was in her neighborhood. Millie had originally asked the oncologist for James to be admitted to the hospital in order to have him transferred to a skilled nursing facility. However, once the OSW suggested the day program, Millie no longer felt the need for James to stay full time at the nursing home. In this case, the OSW's involvement, recommendation, and referral to a community resource resulted in the avoidance of an ED admission.*

Psychiatry

One initiative to avoid ED visits and an additional crisis for patients and families is through partnering or making psychiatry services readily available. The accessibility to a psychiatrist can be helpful in avoiding ED visits for suicide assessment(s). In outpatient cancer centers, if a psychiatrist is not available and a social worker determines that a patient is at risk, the patient would likely be sent to the ED for further assessment. This is not a beneficial allocation of ED resources as it is a potentially avoidable visit that can be upsetting for the patient. If a psychiatrist is on staff at the outpatient cancer center, or psychiatric services are readily available in the community, then ED visits to assess for suicidality may be avoidable.

Health Home Initiative

As more cancer patients are living longer with the disease, cancer is increasingly viewed as a chronic illness [49]. Due to the ongoing evolution of the American healthcare system and changes in reimbursement for services, hospitals will no longer be reimbursed at the same rates for readmissions and ED visits [50]. Therefore, many hospitals are making efforts to lower and contain costs through initiatives that have the potential to decrease readmissions and ED visits. The "Independence at Home" (IAH) initiative for Medicare beneficiaries who have been hospitalized and received rehabilitative services in the past 12 months target those with two or more chronic conditions. This health home initiative offers home-based primary care services aimed at reducing repetitive ED visits and hospitalizations. Under a collaborative

care model of multidisciplinary team members, one IAH initiative utilizes nurses and social workers to do the majority of home visits with the support of physicians [51]. Health homes are one example of a program in which social workers can play a pivotal role to reduce ED visits and readmissions for oncologic patients.

Suggestions for Future Research

More research is needed to understand the optimal role of ED social work in caring for oncologic patients, as well as to identify therapeutic interventions and their effectiveness with patients/families in enhancing their ED experience. There is also a need to identify collaborations and initiatives between ED, oncologic, and palliative social work that have the potential to strengthen the psychosocial care of the patient, avoid duplication of services, and possibly prevent unnecessary ED visits and hospitalizations. As research continues to be done to integrate palliative care in the setting of the ED, social workers, in the fields of emergency medicine, palliative care, and oncologic social work have an opportunity to provide expertise and leadership in the coordination of patient care.

Conclusion

Clinical social workers are trained to conduct a comprehensive biopsychosocial-spiritual assessment of patients and their families, to better inform goals of care, enhance communication, and ensure smooth transitions in care [6, 52]. In working with cancer patients who present to the ED in crisis, the ED social worker can identify psychosocial, financial, and cultural concerns that may impact future medical care. ED, oncologic, and palliative social workers are in key positions to help identify and test new initiatives aimed at strengthening services for oncologic patients throughout the continuum of their illness. Collaboration among these social workers allows for earlier outreach to oncologic patients with unmet psychosocial and concrete needs and supports continuity of care across settings. Attention to the psychosocial needs of oncologic patients and their families can help patients, caregivers, and medical providers optimize the delivery and efficacy of healthcare services while managing the emotional and social aspects of illness [40]. Bridging biomedical and psychological well-being aids in the promotion of better health.

The current healthcare climate focuses on market-driven, cost-containment strategies for the provision of medical care. As such, social workers serve an essential function in the cost-efficient delivery of health care. Social workers are well positioned to contribute to the psychosocial care of oncologic patients in the ED and can identify and coordinate alternative plans of care that may reduce the number of unnecessary ED visits.

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Part II

Prevention

Tobacco Control

8

Steven L. Bernstein

Background

Fifty years after Surgeon General Luther Terry's landmark report on smoking and lung cancer, tobacco use remains the leading cause of death in the United States and the leading cause of preventable death [1]. Worldwide, tobacco use is a growing cause of morbidity and mortality. In many developing countries, it is overtaking infectious diseases as a leading public health hazard. Although great progress has been made in curbing this man-made epidemic, the human and economic costs associated with smoking remain enormous.

In the United States, each year, about 437,000 Americans die from smoking [1]. An additional 41,000 die from exposure to secondhand smoke, largely as a result of living with a smoker. Although smoking prevalence has declined, in 2018, 13.8% of all Americans age 18 and older smoked [2]. The conditions associated with death from secondhand smoke exposure include lung cancer and coronary artery disease, residential fires, and prenatal and perinatal conditions such as sudden infant death syndrome [1]. Smoking is a causative agent in dozens of diseases, enumerated in Surgeon General reports dating back to 1964 and summarized in the most recent 2014 report [1]. These diseases are listed in Table 8.1. Of note, even half a century after publication of the first major Surgeon General's report on smoking, epidemiologic research continues to reveal new associations between smoking and certain cancers, such as renal cell carcinoma, pancreatic cancer, and acute myeloid leukemia.

Emergency departments, visited 138 million times by Americans in 2017 [3], are sites where ED clinicians may conduct opportunistic screening and intervention for tobacco use. ED-initiated tobacco control is effective as found by a 2017 meta-analysis [4] and can be done with a modicum of effort.

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The terms "smoking" and "tobacco use" are often used interchangeably. They are not. "Smoking" refers to the consumption of combustible tobacco. In the United States, that is largely in the form of cigarettes. Other forms of combustible tobacco include cigars, cigarillos, and hookah. In developing countries, bidi and kretek are also popular forms of consuming combustible tobacco.

Smokeless tobacco may be consumed as well, in the form of snus (moist pouched tobacco placed between the lip and gum), chewing tobacco, dip, and snuff (dried, insufflated tobacco). Newer products include nicotine-containing water.

Electronic cigarettes, which consist of a heating element that vaporizes a nicotine-containing solution, which is then inhaled, constitute a new and rapidly growing product. E-cigarettes, as they are known, come in a variety of delivery devices. Most solutions contain nicotine; some do not. There is no uniformity in the design or manufacture of these products, which now come under the regulatory purview of the US Food and Drug Administration (FDA) Center for Tobacco Products. The potential for e-cigarettes to cause illness, including cancer, cardiovascular disease, and addiction, is not well understood. They are currently the subjects of intense study, as well as substantial marketing efforts by the traditional tobacco companies, many of which have acquired e-cigarette manufacturers. Because of the developing science surrounding the health effects of e-cigarettes, they will not be discussed at length.

Diagnosis of Tobacco Use

Tobacco-related illness is common in the ED. A complete listing would include diseases directly caused by smoking, such as chronic obstructive pulmonary disease (COPD), and conditions like asthma whose acuity or treatment is complicated by co-occurring tobacco use. Table 8.1 summarizes the list of tobacco-caused illnesses. An early paper found that about 5% of all ED visits, 7% of all admissions, and 10% of ED charges are attributable to smoking [5].

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Table 8.1 Relative risks for adult mortality from smoking-related diseases, adults 35 years of age and older, based on Cancer Prevention Study II, United States

	Males		Females	
Disease category (ICD-10 code)	Current smoker	Former smoker	Current smoker	Former smoker
Malignant neoplasms				
Lip, oral cavity, pharynx (C00–C14)	10.89	3.40	5.08	2.29
Esophagus (C15)	6.76	4.46	7.75	2.79
Stomach (C16)	1.96	1.47	1.36	1.32
Pancreas (C25)	2.31	1.15	2.25	1.55
Larynx (C32)	14.60	6.34	13.02	5.16
Trachea, lung, bronchus (C33–C34)	23.26	8.70	12.69	4.53
Cervix uteri (C53)	n/a	n/a	1.59	1.14
Kidney and renal pelvis (C64–C65)	2.72	1.73	1.29	1.05
Urinary bladder (C67)	3.27	2.09	2.22	1.89
Acute myeloid leukemia (C92.0)	1.86	1.33	1.13	1.38
Cardiovascular diseases				
Coronary heart disease (I20–I25)				
Persons 35–64 years of age	2.80	1.64	3.08	1.32
Persons ≥65 years of age	1.51	1.21	1.60	1.20
Other heart disease (I00–I09, I26–I28, I29–I51)	1.78	1.22	1.49	1.14
Cerebrovascular disease (I60–I69)				
Persons 35–64 years of age	3.27	1.04	4.00	1.30
Persons ≥65 years of age	1.63	1.04	1.49	1.03
Atherosclerosis (I70)	2.44	1.33	1.83	1.00
Aortic aneurysm (I71)	6.21	3.07	7.07	2.07
Other arterial disease (I72–I78)	2.07	1.01	2.17	1.12
Respiratory diseases				
Influenza, pneumonia (J10–J11, J12–J18)	1.75	1.36	2.17	1.10
Bronchitis, emphysema (J40–J42, J43)	17.10	15.64	12.04	11.77
Chronic airways obstruction (J44)	10.58	6.80	13.08	6.78

From 2014 Surgeon General's report [1]
Note: ICD = International Classification of Diseases

Emergency physicians and nurses screen for smoking irregularly. Tobacco use is more likely to be solicited for patients with conditions that are clearly tobacco-related; less so for others.

There are various ways to screen for tobacco use. In research contexts, a two-question screener is often used. The screener is used by two large annual surveys, managed by the Centers for Disease Control and Prevention: the Behavioral Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS).

The two questions are:

1. Have you smoked at least than 100 cigarettes in your entire life?
   - ☐ No
   - ☐ Yes
   - ☐ Don't know/not sure
   - ☐ Refused
2. Do you now smoke cigarettes every day, some days, or not at all?
   - ☐ Every day
   - ☐ Some days
   - ☐ Not at all
   - ☐ Don't know/not sure
   - ☐ Refused

Individuals who endorse having smoked at least 100 cigarettes/lifetime, and are every- or some-day smokers, are considered to be current smokers. Individuals who endorse at least 100 cigarettes/lifetime, but do not currently smoke, are considered to be former smokers. Those smoking less than 100 cigarettes/lifetime are considered never-smokers.

Of note, these questions do not capture the use of other forms of combustible tobacco, or smokeless forms such as chew, snus, and the newer heat-not-burn cigarettes. Electronic cigarettes (e-cigarettes) and related products, known collectively as electronic nicotine delivery systems (ENDS), constitute a new and growing means of nicotine administration. The oncogenic and pathogenic potential of ENDS is only starting to be studied, although the market share of these products is growing rapidly.

However, in the context of routine clinical care, it is probably sufficient to ask patients if they currently smoke. In our experience, smokers tend to be forthcoming in disclosing

their tobacco use. In the current era of data capture via electronic health records (EHRs), there is typically a structured field in the social history (or elsewhere) to record smoking status. In that case, the provider's choices may be constrained by the responses offered in the "smoking box" of the EHR.

Diagnosis of Tobacco-Related Illness

The list of conditions in Table 8.1 is extensive but does not cover all clinical scenarios in which EM practitioners might discuss smoking with patients. For example, wound healing is often compromised in smokers, with higher risks of poor cosmesis and infection [6]. Injury comprises 18.9% of all ED visits [3], so smokers with injuries are common. Tobacco abstinence should be advised for all smokers with lacerations, fractures, abscesses, and other skin, soft tissue, and musculoskeletal injuries. Discharge summaries generated by electronic medical records should mention tobacco avoidance for patients with traumatic injury.

Illnesses Associated with Tobacco Use

The number of diseases associated with tobacco use is substantial, and Surgeon General reports since 1964 continue to identify new conditions associated with smoking. The list of tobacco-related illnesses, along with their associated relative risks for mortality, is summarized in Table 8.1.

Note that many of these conditions are commonly seen in the ED. These are largely the cardiovascular diseases, such as chest pain, acute coronary syndromes including myocardial infarction and unstable angina pectoris, and respiratory diseases including pneumonia, influenza, exacerbations of chronic bronchitis and emphysema, and asthma. Patients with cancer are, of course, seen in the ED. They generally present with a complication of treatment or the cancer itself.

Cancer is occasionally, albeit rarely, diagnosed de novo in the ED. It is important to note that these diagnoses are presumptive, because no tissue diagnosis has yet been made.

Some possible scenarios in which cancer may be presumptively diagnosed include:

- A heavy smoker who presents with a cough, dyspnea, or weight loss and has a new pulmonary mass seen on chest x-ray
- A heavy smoker who presents with marked weight loss, progressive difficulty swallowing, and a mediastinal mass contiguous with the esophagus seen on chest x-ray or CT scan
- A postmenopausal woman who presents with vaginal bleeding
- A person who presents with fever and generalized bleeding and is found to be thrombocytopenic with many blast cells in the peripheral blood smear

Of note, tobacco use also is relevant in the ED management of conditions not formally associated with smoking. For example, acute exacerbations of asthma are commonly treated in the ED [7]. Although asthma is not caused by smoking, tobacco use is common among ED asthmatics. It increases the frequency and severity of attacks and prolongs the duration of the exacerbation. Another example would be the management of cellulitis in the foot of a person with diabetes and concurrent smoking. Smoking contributes to the development of peripheral vascular disease and may impair wound healing.

Emergency Department Treatment of Tobacco Dependence

Because of tobacco's great burden of illness and death, its disproportionate use by individuals of low socioeconomic status (SES), and the heavy use of EDs by low SES individuals, the ED has been regarded as an opportune venue in which to initiate treatment for smoking. The accumulating evidence of tobacco's causative role in ED-managed illness and injury has led to its inclusion in the core curriculum of the specialty [8]. Much of the research in this area has entailed understanding provider facilitators and barriers to ED-initiated interventions for smoking.

The general approach to ED-initiated intervention for smoking is adapted from the model known as Screening, Brief Intervention, and Referral to Treatment (SBIRT) [9]. SBIRT entails using one or two questions to identify an individual with a risky health behavior, offering an abbreviated form of motivational interview [10] to promote behavior change and then referring to an appropriate source of aftercare. Initially developed to identify and intervene with persons with alcohol use disorders, SBIRT has been endorsed by the Substance Abuse and Mental Health Services Administration and other professional bodies for use in the ED [11]. ED-based studies with more intensive interventions have generally offered a combination of SBIRT (tailored for smokers) and motivational interviewing.

A newer approach to ED-initiated interventions known as Screening, Treatment Initiation, and Referral (STIR) [12] incorporates medication management into the ED intervention. In the case of smoking, a STIR-informed approach would include the initiation in the ED of nicotine replacement therapies such as patches and gum. Several studies have demonstrated the efficacy of STIR for tobacco dependence [13, 14] and buprenorphine for managing opioid

dependence [15]. STIR capitalizes on the teachable moment often found in the ED visit, when patients may be motivated to change an unhealthy behavior [16].

There are numerous evidence-based treatments for tobacco dependence. These may be divided into two broad categories: medication and counseling. Each is effective; used in combination, they provide even greater efficacy.

There are seven FDA-approved medications: nicotine patch, gum, lozenge, nasal spray, and inhaler, plus varenicline and bupropion. Counseling strategies with proven efficacy include one-on-one in-person sessions, group counseling, and telephone quitlines. The evidence base supporting these treatments is reviewed extensively in the 2008 Public Health Service's guideline on tobacco dependence treatment and in the 2014 Surgeon General's report on smoking.

Of note, quitlines are widely available in all 50 states. They can be accessed by a single phone number: 1-800-QUIT-NOW. Services vary somewhat from state to state, but as a rule include counseling by a trained provider, provision of written materials, starter doses of nicotine replacement, web-based services, and, increasingly, smartphone-based texting services. Quitlines are open 7 days a week, and languages other than English are available. Referrals can be made by providers or smokers. There is no cost to individuals or health systems, and insurance is not needed. Additional information is available at www.naquitline.org, the home page of the North American Quitline Consortium.

Most smoking cessation counseling uses principles of motivational interviewing or cognitive behavioral therapy. Of note, neither hypnosis nor acupuncture has demonstrated efficacy.

These treatments are summarized in Table 8.2.

The pharmacotherapy of nicotine dependence treatment is straightforward. Smokers who consume five or more cigarettes daily are good candidates for treatment. Medication is typically begun with a single agent, usually the nicotine patch or gum. A single cigarette contains 1–3 mg of nicotine, which can be used to guide dosing. In general, nicotine should be replaced milligram-for-milligram. A 21-mg patch, applied daily, would be a typical treatment for someone who smokes ten or more cigarettes daily. Higher dosing or additional forms of nicotine replacement therapy (NRT) may be added if the patient experiences cravings. Recent studies suggest combination therapy, using both long-acting and short-acting agents (e.g., patch and gum or nasal spray or inhaler), may be more effective than monotherapy. The reason is that transdermal nicotine generally does not replace enough nicotine to prevent cravings and other symptoms of withdrawal. NRT products that cross the blood-brain barrier quickly and easily can offer rapid relief for smokers with cravings.

Bupropion is a drug whose mechanism of action is incompletely understood. It was initially approved for treatment of mood disorders but also shows efficacy in smoking cessation. Varenicline is an interesting drug that blocks nicotinic receptors in the brain that mediate reward and craving. It is an agonist-antagonist. Varenicline prevents nicotine from binding to receptors but stimulates the release of a small amount of dopamine, generally sufficient to prevent symptoms of withdrawal. These drugs are beyond the scope of practitioners of emergency care and are not indicated for initiation in the ED.

The clinical trials of ED-initiated tobacco dependence treatment are summarized in Table 8.3 [13, 17–23, 25]. Most were single-institution studies with modest sample sizes and limited methodologic rigor. More recent studies from the 2010s used larger sample sizes, biochemical confirmation of tobacco abstinence at follow-up, and rigorous methods to minimize attrition and found various interventions to be efficacious.

A study from 2015 [13] found that a multicomponent intervention was able to produce a statistically significant higher rate of tobacco abstinence in subjects at the primary endpoint, 3 months, compared to controls. At 1 year, the effect attenuated but nearly reached statistical significance. The intervention consisted of provision of 6 weeks of nicotine patches and gum, initiation of the patch in the ED, a brief motivational interview (10–15 min) by a trained interventionist, a referral faxed to the state smokers' quitline, a phone call 2–3 days after enrollment, and a smoking cessation brochure. This study was the first to demonstrate the efficacy of ED-initiated tobacco dependence treatment. Although efficacious, the intervention has limited generalizability because of the use of nonclinical personnel to perform the motivational interview and the provision of a substantial supply of nicotine replacement medication.

An additional limitation of this study was the inability to disaggregate the effects of individual components, given the intervention was delivered as a package. To identify the efficacy of individual components, as well as interactions between components, the investigators conducted a $2 \times 2 \times 2 \times 2$ factorial trial using the multiphase optimization strategy (MOST) [27]. MOST studies use iterative approaches to identify packages of effective intervention components, subject to a cost constraint. In this study, 1056 adult smokers were enrolled and randomized to receive up to four interventions: a brief motivational interview, 6 weeks of nicotine gum and patches with the first dose applied in the ED, an active referral to a smokers' quitline, and enrollment in the SmokefreeTXT texting program of the National Cancer Institute. Each intervention was "on" or "off" for each participant, so the trial had 16 conditions.

At 3 months' follow-up, both the motivational interview and the nicotine replacement therapy were found to increase abstinence (motivational interview 13.5% vs. 8.9% [$P = 0.02$]; NRT, 14.4% vs. 8.0% [$P = 0.001$]) [14]. Neither

Table 8.2 Tobacco dependence treatment medications

Products OTC	Dosage	Duration	Precautions	Adverse effects	Patient education
Nicotine patch 21 mg 14 mg 7 mg	One patch per day. >10 cpd: 21 mg 4 weeks, 14 mg 2 weeks ≤10 cpd: 14 mg 4 weeks 7 mg 2 weeks	8–12 weeks	Do not use if patient has severe eczema or psoriasis Caution within 2 weeks of MI	Local skin reaction Insomnia	Apply each day to clean, dry, hairless skin Focal rash is common: Rotate site daily Available without prescription.
Nicotine gum 2 mg 4 mg	First cigarette ≤ 30 min after waking: 4 mg First cigarette > 30 min after waking: 2 mg 1 piece every 1–2 h	12 weeks	Caution with dentures Do not eat or drink 15 min before or during use Limit 24 in 24 h	Mouth soreness Stomachache Hiccups	*DO NOT CHEW LIKE ORDINARY GUM* Alternate chewing and "parking" between the cheek and gum (chew until mouth tingles and then park for 1 min, continue for 30 min) Nicotine absorbed across the buccal mucosa Avoid food and acidic drinks before and during use Available without prescription
Nicotine lozenge 2 mg 4 mg	First cigarette ≤ 30 min after waking: 4 mg First cigarette > 30 min after waking: 2 mg 1 piece every 1–2 h	12 weeks	Do not eat or drink 15 min before use One lozenge at a time Limit to 20 in 24 h	Heartburn Local irritation of the mouth and throat Coughing Hiccups	*DO NOT BITE, CHEW, or SWALLOW* Dissolve in mouth slowly Each lozenge takes 20–30 min to dissolve Avoid food and acidic drinks before and during use Available without prescription
Nicotine inhaler Nicotrol Inhaler®	6–16 cartridges/day Each cartridge = 2 cigs Use 1 cartridge q 1–2 h	6 months; taper	Reactive airway disease	Mouth and throat irritation Cough	Patient is not to puff like a cigarette. Gentle puffing recommended Absorption via the buccal mucosa Avoid food and acidic drinks before and during use
Nicotine nasal spray Nicotrol NS®	1–2 sprays each nostril/h 8–40 doses/day	3–6 months; taper	Not for patients with asthma	Nasal irritation Sneezing Cough Teary eyes	Instruct patient to tilt the head back and spray Tolerance to local adverse effects develops first week after use
Bupropion SR150 Zyban® or Wellbutrin®	Start 1–2 weeks before quit date Days 1–3: 150 mg each morning Days 4–end: 150 mg BID	2–6 months	Contraindications: Seizure disorder Current use of MAO inhibitor Eating disorder Alcohol dependence Head trauma	Insomnia Dry mouth Anxiety	Take second pill early evening to reduce insomnia Never double dose if miss a pill
Varenicline Chantix®	Start 1 week before quit date 0.5 mg/day for 3 days and then 0.5 mg BID for the next 4 days After first 7 days 1 mg/BID	3–6 months	Persons with kidney problems require dose adjustment Serious psychiatric illness	Nausea Insomnia Abnormal dreams	Take after eating and with water (full glass) Never double dose. Take missed dose as soon as remembered. If close to next dose wait and take at regular dose time Nausea is usually transient. If nausea persists, dose reduction is recommended

OTC over the counter, *MI* myocardial infarction, *MAO* monoamine oxidase

the quitline nor the texting program was efficacious. No interactions were noted. This study was the first to identify individually effective components of ED-initiated tobacco control. Future work for ED-based tobacco treatment should focus on the scalability of these interventions.

Table 8.4 reviews the components of an effective ED-initiated tobacco intervention. The individual components are all supported by evidence from high-grade clinical trials in various settings, with at least one high-quality ED trial to support their use.

Table 8.3 Benefit of emergency department-initiated tobacco control compared with control condition on tobacco-use results of individual studies ($n = 11$) and meta-analyses, by follow-up time[a]

	Mantel-Haenszel relative risk (95% confidence interval)			
Year of publication, study	1 month	3 months	6 months	12 months
2000, Antonacci and Eyck [17]	–	–	0.33 (0.01–7.74)[b]	–
2000, Richman et al. [18]	–	1.14 (0.36–3.57)	–	–
2007, Horn et al. [19]	–	–	0.83 (0.05–12.77)	–
2007, Schiebel and Ebbert [20]	–	2.00 (0.20–20.33)	9.00 (0.52–156.91)[b]	–
2008, Bock et al. [21]	1.64 (1.04–2.56)	1.35 (0.86–2.12)	1.04 (0.64–1.68)	–
2008, Boudreaux et al. [22]	–	1.86 (0.25–13.91)	–	–
2009, Neuner et al. [23]	1.30 (0.79–2.15)	1.13 (0.75–1.69)	1.14 (0.81–1.61)	1.25 (0.91–1.72)
2011, Anders et al. [24]	–	0.62 (0.21–1.83)	–	–
2011, Bernstein et al. [25]	–	1.12 (0.66–1.91)	–	–
2013, Cheung et al. [26]	1.69 (0.56–5.08)	1.93 (0.66–5.63)	0.64 (0.27–1.55)	0.55 (0.18–1.66)
2015, Bernstein et al. [13]	–	2.49 (1.49–4.16)	–	1.38 (0.97–1.98)
Meta-analyses	1.49 (1.08–2.05) [$P = 0.01$]	1.38 (1.12–1.71) [$P = 0.003$]	1.09 (0.84–1.41) [$P = 0.54$]	1.26 (1.00–1.59) [$P = 0.05$]

Adapted from Lemhoefer et al. [4]

[a]This systematic review and meta-analysis updates a previous review and includes publications published between October 4, 2010, and May 15, 2015

[b]0.5 added to all cells of the 2 × 2 table in calculating the relative risks to avoid degeneracy caused by sampling zero counts

Table 8.4 Components of an effective ED-initiated intervention for tobacco dependence

Component	Comments
Counseling	Brief counseling intervention employing principles of motivational interviewing; cognitive behavioral treatment may be efficacious
Medication	Provision of at least 4 weeks of nicotine replacement therapy. Combining short- and long-acting forms (e.g., patch and gum) likely to be more efficacious than monotherapy
Post-discharge treatment: quitline, texting	Aftercare should extend at least 30 days beyond visit. Active referral to state smokers' quitline, via fax or electronic health record, may achieve that. Newer interventions such as use of cellphone texting warrant further study
Interventionist	Ideally, a nonclinical individual, such as a health promotion advocate or health educator. Can be delivered by physicians, midlevel providers, and nurses, but constraints of time and clinical burden are substantial

Cost

Tobacco dependence treatment is among the most inexpensive, most cost-effective interventions in clinical medicine [28]. Integrating tobacco dependence screening, treatment, and referral into ED clinical workflows can be quite inexpensive. Several models of practice are available. The cheapest is to allow providers—physicians, nurses, and midlevel practitioners—to perform the screening as part of routine clinical care. Brochures advertising the state tobacco quitline, generally available from health departments in bulk at little to no cost, can be distributed to smokers. Advice to quit, call the quitline, or perhaps visit a locally available smoking cessation clinic can be templated and added to discharge summaries. Directed referrals to quitlines via fax can be made by clinical or clerical personnel. Some electronic medical records are integrating quitline referrals into their order sets for tobacco dependence [29].

A more intensive, and expensive, model of care entails placing lay educators or health promotion advocates in EDs to screen patients for tobacco use and other risky health behaviors [30]. These models are effective in identifying and referring patients, but their impact on long-term abstinence rates is unclear.

Conclusion

Tobacco use is widely prevalent in emergency department patients, and tobacco-related illness is a common reason for presentation. Recent evidence suggests that ED initiation of nicotine replacement therapy and behavioral counseling are independently effective in promoting sustained tobacco abstinence. As a result of the accumulating evidence regarding the efficacy of ED-initiated tobacco control, both the US Public Health Services' clinical practice guideline [31] and a report by the Institute of Medicine [32] recommend EDs as effective loci for tobacco screening and treatment. Tobacco use carries a sufficient burden of illness and death to warrant routine screening and intervention in ED patients. Future work should focus on finding ways to disseminate and implement these effective interventions.

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Problem Drinking

9

Edouard Coupet Jr. and Federico E. Vaca

Case Study

Linda is a 52-year-old woman who presents to the emergency department (ED) with a chief complaint of a forehead laceration following a fall down a flight of stairs. While she was at home, she states that she had consumed a half a pint of vodka in the afternoon. While traveling down the stairs, she missed the last step, fell, struck her head, and sustained a small laceration to her forehead. She denies any other complaints and otherwise is nontoxic appearing. Her past medical history includes breast cancer, which was diagnosed 4 years ago, and hypertension. While in the ED, the physician orders a CT scan of her head which found no evidence of acute intracranial injury. The nurse administers tetanus prophylaxis and the physician repairs Linda's laceration. While repairing her laceration, the physician finds out that Linda drinks at least a pint of vodka every day. The physician soon determines that she appears clinically sober and almost ready for discharge. However, there is concern about Linda's heavy alcohol use. The physician notifies the social worker who comes to talk to Linda about her alcohol use and drinking pattern. A medical chart review reveals that Linda has presented to the ED three times in the last year for various falls. After further brief discussion and evaluation, it is determined that Linda meets the criteria for moderate alcohol use disorder (AUD). The social worker informs and educates Linda about unhealthy drinking and drinking patterns that are associated with AUDs. She further assesses her willingness to seek AUD treatment. Linda states she is not interested in seeking inpatient treatment at this time but is willing to accept a referral for outpatient treatment services. Linda is discharged from the ED and provided a follow-up appointment at a specialized treatment clinic that can help manage her AUD.

Background

Alcohol consumption plays a substantial role in human culture worldwide [1, 2]. It has been estimated to account for approximately 4% of the total global disease burden [3]. In 2016, it was the seventh leading risk factor for death, globally [4]. In the USA, similar to many other industrialized countries, alcohol use disorders (AUDs) remain among the most common, yet undertreated, behavioral health disorders [5]. This is particularly important because individuals with AUD contribute to nearly half of alcohol-related diseases, including various cancers and injuries [6].

Alcohol use most commonly begins during adolescence [7–10]. As youth progress from early to late adolescence, alcohol use typically increases. According to data from the Monitoring the Future National Survey Results on Drug Use, in 2018, 8% of 8th graders reported alcohol use, while 30% of 12th graders reported alcohol use in the past month [11]. Moreover, the earlier youth begin to use alcohol, the higher their risk is for alcohol-related adverse consequences. In one study of over 27,000 current and former individuals who have drank, an estimated 40% of individuals who started drinking at age 14 or younger developed alcohol dependence over their lifetime. The rate declined to nearly 10% when the individual started drinking at age 20 or older [12].

Previous literature has characterized four individual trajectory groups (i.e., low, high, increasing, and decreasing) of alcohol use based upon age at onset of drinking and drinking patterns [8, 13–15]. The "low" group consisted of individuals who either drank lightly or abstained completely across the entire adolescent-adult lifespan. The "high" group consisted of adolescents who drank heavily at a late-onset or chronically across the adolescent-adult lifespan. The

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"increasing" group consisted of adolescents who began drinking heavily in their late adolescence or emerging adult years. Shortly after this developmental period, their alcohol use declined. The final group of "decreasing" individuals began drinking heavily early in their adolescence and declined as they transitioned into late adolescence.

In 2018, results from the National Survey on Drug Use and Health (NSDUH) showed that nearly 140 million Americans aged 12 or older drank and 67 million reported binge drinking alcohol in the past month. Among adolescents aged 12–17, 4.7% reported binge drinking in the past month. Among young adults aged 18–25 and adults aged 26 and older, 34.9% and 25.1% reported binge drinking alcohol in the past month, respectively. Approximately 15 million Americans aged 12 or older meet the criteria for AUD as defined by the *Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)* criteria for abuse or dependence. An estimated 1.6% of adolescents aged 12–17 meet the criteria for AUD. Among adults, 10.1% of those aged 18–25 and 5.1% of those aged 26 and older meet the criteria for AUD [16].

A variety of public health problems are either directly or indirectly caused by excessive alcohol consumption, including hepatic and pancreatic diseases, cancers, diabetes, suicide, cardiovascular disease, infectious diseases, and both intentional and unintentional injuries [17]. Regulation of alcohol sales and taxes on alcoholic beverages has been instituted at both federal and state levels to mitigate excessive alcohol consumption and alcohol-related disease. There is strong evidence to support these efforts [18–23]. One study determined that alcoholic beverage tax increases in 1983 and 2002 in Alaska which reduced the rate of death from alcohol-related diseases by 29% and 11%, respectively [24]. A systematic review of literature that evaluated the effect of alcohol purchasing hours on several alcohol-related harms determined that regulation of these hours can reduce alcohol-related hospitalizations and injuries, such as motor vehicle collisions (MVCs) [25].

Research has informed a spectrum of drinking levels. According to the 2015–2020 Dietary Guidelines for Americans, a standard drink is defined as 1.5 oz (45 mL) of 80-proof spirits, 12 oz of beer, or 5 oz of table wine. Each of these contains approximately 14.5 g of absolute ethanol. For those of legal drinking age, moderate alcohol consumption is defined as one drink per day for women and up to two drinks per day for men. Binge drinking is defined as a pattern of alcohol consumption that increases the blood alcohol concentration (BAC) to 0.08% or greater. This usually happens after four drinks for women and five drinks for men within 2 h. Heavy alcohol use is defined as greater than four drinks a day for men or greater than three drinks a day for women. Both binge and heavy alcohol use increase an individual's risk of adverse and negative consequences [26].

In this chapter, we will review common emergency department (ED) encounters for alcohol-related diseases and injuries, the identification and diagnosis of AUD, the ED approach to prevention of AUD, and the role of ED-based alcohol screening, brief intervention, and referral to treatment (SBIRT) in preventing alcohol related-cancers.

ED Encounters for Alcohol-Related Disease and Injury

Acute Conditions Related to Alcohol Use

From 2006 to 2014, the number of alcohol-related ED encounters in the USA increased by nearly 62% [27]. The unhealthy consumption of alcohol is a substantial burden on EDs, causing both injury and disease. Injury is one of the most common causes of alcohol-related ED encounters, accounting for up to 50% of all alcohol-related ED encounters in one study [28]. Alcohol has a well-established link to many types of unintentional injuries, particularly because of its psychomotor impairing effects [6, 29]. A meta-analysis of 28 articles of acute alcohol consumption and injury demonstrated a strong dose-response relationship of acute alcohol consumption and both MVC and non-MVC injuries [30]. Moreover, drivers who drink alcohol, yet are not legally impaired, cause thousands of deaths as well [31]. In a multisite prospective cohort study of both intoxicated and non-intoxicated injured drivers, alcohol was found to be a significant predictor of morbidity post-injury [32]. Previous research shows that younger drivers who have consumed alcohol are at highest risk for a fatal MVC because of their lower alcohol tolerance and relative driving inexperience [24, 33, 34]. Prior consumption of alcohol is also highly associated with increased injury severity, longer hospitalization, and higher healthcare costs in bicycle-related injuries presenting to the ED [35].

Intentional injuries, which commonly present to the ED, have an even greater association with alcohol use [36–38]. Alcohol consumption is well-known to increase aggressive behaviors and decrease inhibition [39]. Existing literature shows a strong link between alcohol use and interpersonal violence [36–38, 40, 41]. In a meta-analysis of 37 EDs across 18 different countries, 44.1% assault-related injuries were attributed to alcohol use, the highest for all types of injuries [40]. Another ED-based study found higher rates of a positive BAC in those who suffered an assault-related injury compared to those who were injured due to other causes [42].

Although the relationship is not as strong as that for non-partner violence, there is evidence to support the link between alcohol and intimate partner violence [43, 44]. A meta-analysis determined a small to moderate effect size for the

link between alcohol use and male-to-female partner violence and a small effect size for female-to-male partner violence [43]. Previous literature also demonstrates an association between alcohol use and behavioral health disorders, which increase the risk for suicide [45, 46].

Chronic Conditions Related to Alcohol Use

In the USA, the number of ED encounters for chronic conditions related to alcohol use increased by nearly 76% between 2006 and 2014. Harmful alcohol use, as indicated by the World Health Organization (WHO), was associated with 48% of liver cirrhosis cases [39]. There is substantial evidence to support the deleterious effects of alcohol on liver function and its role in the development of liver diseases seen in the ED such as cirrhosis, hepatic encephalopathy, and hepatitis [47–49]. In a prospective study of middle-aged women in the UK, daily alcohol consumption, not paired with meals, was associated with a twofold increase in liver cirrhosis. Moreover, patients with alcohol-related liver disease who have refrained from alcohol use experienced an increase in their life expectancy [49]. Another prospective population-based study demonstrated that the relative risk of developing alcohol-related liver disease significantly increased when women drank 7–13 and men 14–27 alcoholic beverages per week [50]. Evidence shows that current recommendations for safe alcohol consumption thresholds may be too high, further contributing to the increased alcohol-related disease burden and harm [51, 52].

Since the turn of the century, there is increasing evidence that supports the casual link between alcohol consumption and cancer [53–56]. Alcohol consumption is linked to cancers of the head and neck, liver, gastrointestinal (GI) tract, and for women, breast [57]. Although the mechanism by which it causes cancer is not well understood, alcohol is believed to have several different carcinogenic mechanisms which likely differ by organ site. Acetaldehyde, the primary toxic metabolite of alcohol, is believed to alter deoxyribonucleic acid (DNA) strands [53, 57, 58]. Alcohol also reduces the blood concentration of important antioxidants including vitamins A and E, folic acid, thiamine, zinc, and iron. Additionally, it suppresses the immune system and can potentiate the effects of other carcinogenic agents [53]. Fortunately, evidence suggests stopping alcohol consumption can reduce the risks of developing certain types of cancers [59].

Along with tobacco use, alcohol consumption is one of the largest risk factors for cancers of the head and neck [60]. Previous research demonstrates that alcohol accounts for 26.4% of lip and oral cancers, 30.5% of all pharyngeal cancers, 21.6% of laryngeal cancers, and 16.9% of esophageal cancers [61]. Evidence also supports a dose-dependent relationship between alcohol use and head and neck cancers. In one study, participants who drank more than seven alcoholic beverages per day had four times the risk of developing cancers of the head and neck compared to those who abstained from drinking [62]. A meta-analysis of alcohol use and risk of head and neck cancers demonstrated that individuals who drank lightly, moderately, and heavily had relative risks of developing cancers of the head and neck of 1.13, 1.83, and 5.13, respectively [63]. There is also evidence to suggest that individuals who continue to drink, with a primary head and neck cancer diagnosis, are at increased risk of both primary cancer recurrence and development of a second primary cancer. A multisite study of more than 4000 individuals with head and neck cancer showed that participants who drank more than one alcoholic beverage per day had an increased risk of developing a second primary cancer [64]. A single-site retrospective study of individuals with a primary head and neck cancer diagnosis showed that consuming 8–14 drinks per week was associated with an elevated risk of recurrence.

Heavy alcohol use is among the strongest risk factors for developing hepatocellular carcinoma (HCC) [65, 66]. Alcohol is believed to be both directly responsible for HCC and indirectly by causing liver cirrhosis, a well-known risk factor for HCC [61]. Alcohol has been proposed to cause oxidative stress, leading to the generation of free oxygen radicals and consequently, DNA damage [61]. A previous epidemiological study suggests that drinking more than 80 g/day for at least 10 years substantially increases the risk of developing HCC [67]. Evidence also shows a synergistic effect when heavy alcohol consumption is paired with the hepatitis B or C virus infection. A case-control study of 115 patients with HCC demonstrated that those who report heavy alcohol use and have chronic hepatitis had an odds ratio (OR) of 53.9, compared to an OR of 2.4 with alcohol alone or 19.1 with the virus alone [68].

Although the evidence may not be as strong as that for other malignancies, there is evidence to support an association between alcohol use and cancer of parts of the GI tract, notably the esophagus, colon, and rectum. Up to 75% of cases of esophageal cancer can be attributed to alcohol use. Chronic alcohol consumption is understood to increase the esophageal mucosa's susceptibility to carcinogens [61]. Previous research shows a strong link between esophageal squamous cell carcinoma and alcohol consumption [69]. However, research does not support the same relationship for gastric cancer. A review of over 40 epidemiological studies of gastric cancer and chronic alcohol use did not find any association between the two [70]. Numerous studies suggest an increasing dose-dependent relationship between alcohol use and colorectal cancer [71]. A review of over 50 cohort and case-control studies found increased association between alcohol use and colorectal cancer by a factor of 2 [72].

The International Agency for Research on Cancer determined alcohol consumption to have a causal relationship to breast cancer, which exists in both premenopausal and postmenopausal women [69]. Existing literature suggests a 7–10% increase in risk for breast cancer for every 10 g (~1 drink) of alcohol/day consumed by an adult woman. This relationship has even been found in women who drink alcohol lightly [73–76]. A proposed mechanism behind this relationship appears to be the increased estrogen levels found in women who drink [75]. Alcohol has also been linked to recurrence of breast cancer and increased mortality from the disease. In a review, having more than 6 g of alcohol/day was associated with an increase in recurrence of and death from breast cancer. This relationship was determined to be even stronger in postmenopausal and obese women [77].

Special Considerations for Health Disparities

Existing data of alcohol consumption patterns demonstrate differences and disparities across ethnic and racial minority groups. According to the NSDUH, reported past month use of any alcohol in individuals aged 12 and older was highest in Whites (57.7%), followed by Blacks (43.6%), Latinos (43%), Native Hawaiians/Pacific Islanders (38.4%), American Indians/Alaska Native (37.3%), and Asians (34.5%). However, Native Hawaiians/Pacific Islander populations were most likely to report heavy alcohol use in the past month (8.9%), while Asian populations reported the lowest rates (2%) [16]. White and Native American populations have the highest risk for developing AUD [78].

Once alcohol dependence develops, Black and Latino populations have the highest rates of recurrent or persistent dependence [79]. A review of 19 studies of racial/ethnic disparities and alcohol-attributable injury determined that Native Americans had the highest rate of alcohol-attributable injuries such as MVCs, self-injury, and falls compared to other racial/ethnic groups [80]. Black and Latino populations are also at greatest risk for developing alcohol-related liver disease [81]. Previous research suggests that gaps in alcohol treatment utilization are highest in Latino populations, particularly among those primarily Spanish-speaking [82–85]. Evidence demonstrates that alcohol treatment programs should take these socioeconomic and cultural factors into consideration when addressing disparities among racial/ethnic groups [86–89].

Identification and Diagnosis of Alcohol Use Disorder

Alcohol-Related Conditions

There were over 138 million ED encounters in the USA in 2017. Alcohol use contributed to a substantial portion of these encounters. Over 4.2 million ED encounters were related to alcohol misuse, abuse, or dependence [90]. Furthermore, acute alcohol-related disorders, such as injury, are among the leading causes of alcohol-related ED encounters. The list of all of the International Classification of Diseases, Tenth Revision (ICD-10), alcohol-related conditions an ED clinician may encounter is provided in Table 9.1.

Diagnosis of Alcohol Use Disorder

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), criteria for diagnosis of AUD has shifted to a broader spectrum based on severity as compared to the dual model of alcohol abuse and dependence within the DSM-IV. In the DSM-IV, there were four diagnostic criteria for alcohol abuse and seven for dependence. In the DSM-5, the diagnostic criteria, which highlight craving, loss of control, tolerance, and withdrawal, have increased to 11 (Box 9.1). Individuals with two to three criteria meet the diagnosis of mild AUD; individuals with four to five, moderate; and individuals with six or more,

Box 9.1 *Diagnostic and Statistical Manual of Mental Disorders*, **Fifth Edition (DSM-5): Alcohol Use Disorder**

1. Alcohol-related failure to fulfill obligations
2. Recurrent drinking in hazardous situations
3. Continued drinking despite problems
4. Tolerance
5. Withdrawal
6. Drinking more or more often than intended
7. Unable to quit/cut back drinking
8. Spent a lot of time drinking/recovering
9. Gave up important activities due to drinking
10. Continued drinking despite consequences
11. Craving
Mild alcohol use disorder (AUD): 2–3 criteria required
Moderate AUD: 4–5 criteria required
Severe AUD: ≥6 criteria required

Table 9.1 ICD-10 codes for alcohol-related conditions

Group	ICD-10 code	Disorder
Acute conditions	F10.0	Mental and behavioral disorders due to use of alcohol, acute intoxication
	R78.0	Finding of alcohol in blood
	T51.0	Toxic effects of ethanol
	V12–V14 (0.3–0.9), V19.4–V19.6, V19.9, V20–V28 (0.3–0.9), V29–V79 (0.4–0.9), V80.0–V86 (0.0–0.3), V87.0–V87.9, V89.2, V89.3, V89.9	Road traffic injuries-non-pedestrian
	V02–V04 (0.1,0.9), V06.1, V09.2, V09.3	Road traffic injuries-pedestrian
	W00–W19	Fall injuries
	W65–W74	Drowning
	W78–W79	Aspiration
	W24–W31, W45, W60	Occupational and machine injuries
	X00–X09	Fire injuries
	X78–X79, Y87.1	Assault
	X85–Y09, Y87.1	Child abuse
	X60–X84, Y87.0	Suicide
	X45	Accidental poisoning by and exposure to alcohol
	X65	Intentional self-poisoning by and exposure to alcohol
	Y15	Poisoning by and exposure to alcohol, undetermined intent
Chronic conditions	C01–C06, C09–C10, C12–C14	Oropharyngeal cancer
	C15	Esophageal cancer
	C22	Hepatocellular cancer
	C32	Laryngeal cancer
	C50	Female breast cancer
	E24.4	Alcohol-induced pseudo-Cushing's syndrome
	F10.1	Mental and behavioral disorders due to use of alcohol, harmful use
	F10.2	Dependence syndrome
	F10.3	Withdrawal state
	F10.4	Withdrawal state with delirium
	F10.5	Psychotic disorder
	F10.6	Amnesic syndrome
	F10.7	Residual and late-onset psychotic disorder
	F10.8	Other mental and behavioral disorders
	F10.9	Unspecified mental and behavioral disorder
	G31.2	Degeneration of nervous system due to alcohol
	G62.1	Alcohol polyneuropathy
	I42.6	Alcoholic cardiomyopathy
	K29.2	Alcoholic gastritis
	K70.0	Alcoholic fatty liver
	K70.1	Alcoholic hepatitis
	K70.2	Alcohol fibrosis and sclerosis of the liver
	K70.3	Alcoholic cirrhosis of the liver
	K70.4	Alcoholic hepatic failure
	K70.9	Alcoholic liver disease, unspecified
	K85.2	Alcohol-induced acute pancreatitis
	K86.0	Alcohol-induced chronic pancreatitis
	O03	Spontaneous abortion
	O36.5, P05, P07	Low birth weight

severe [91]. As a result of these changes in the DSM-5, some individuals may either have gained, lost, or changed in severity. The DSM-5 also removed alcohol-related legal problems and replaced it with the criteria of craving.

ED Approach to Prevention of Alcohol Use Disorder

Since many individuals seek emergency care for both acute and chronic alcohol-related concerns, the ED is the

ideal setting for the clinicians to approach and engage their patients regarding their alcohol use. With their patient's permission, ED clinicians should use this opportunity to discuss unhealthy alcohol use in an open, honest, nonconfrontational, nonjudgmental manner. To promote behavior change, ED clinicians should use health promotion, which is defined by WHO as "the process of enabling people to increase control over and to improve their health" [92]. For those who abstain or who are moderate alcohol consumers, this includes education about unhealthy/high-risk drinking and reinforcement of existing healthy behaviors. Individuals with high-risk drinking should be encouraged to reduce their drinking, ideally below the high-risk limits or less if possible. Federal dietary guidelines, endorsed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), clearly state that a person who does not drink alcohol should not start drinking for any reason [26].

Some individuals who report unhealthy or high-risk drinking may not be prepared to abstain from alcohol use completely. As an alternative to promoting abstinence, ED clinicians should provide harm reduction education. Harm reduction is a strategy to minimize the acute harms associated with alcohol intoxication [93–95]. It includes reducing alcohol consumption, avoiding drinking and driving, and changing drinking patterns. A systematic review of 63 studies of reduced alcohol use showed that harm reduction strategies can decrease alcohol-related injuries, slow progression of alcohol-related diseases such as cirrhosis and cardiomyopathy, and reduce withdrawal symptoms [96].

A substantial amount of literature has evaluated screening and providing an ED-based intervention for unhealthy alcohol use. Over two decades ago, a framework for intervention known as screening, brief intervention, and referral to treatment (SBIRT) was developed and tested in both acute and primary care settings for high-risk behaviors such as substance use. SBIRT involves a psychosocial intervention which utilizes principles of motivational interviewing to encourage individuals with unhealthy alcohol use to pursue treatment. The intervention, more specifically the brief negotiated interview (BNI), relies upon a patient-centered discussion that assesses their willingness to reduce their alcohol use toward healthier limits. It utilizes principles of both harm reduction and health promotion. The American College of Emergency Physicians, the Committee on Trauma of the American College of Surgeons, and the Emergency Nurses Association have all recommended SBIRT for addressing unhealthy alcohol use in their respective clinical settings [97–99].

There is modest evidence to support the effectiveness of ED alcohol SBIRT in reducing alcohol use and alcohol-related consequences in the ED [93, 100–103]. A 2007 systematic review of 13 studies found SBIRT did not have any effect on quantity/frequency of drinking at 12 months and was inconclusive at 3 months. However, it did find a 41% reduction in the odds of alcohol-related injury at 6 and 12 months following the initial ED encounter [104]. A more recent systematic review of 35 articles that evaluated the effect of a brief intervention on ED patients who were screened as high-risk for AUD showed a short-term effect in reducing alcohol consumption in those who drank low or moderately [101]. Previous research also shows that ED SBIRT for alcohol use is cost-effective [105].

The BNI of SBIRT has been developed and tested in numerous different modalities including in-person, computerized, and by smartphone (Box 9.2). A previous concern about SBIRT was that characteristics of the BNI and patient had not been evaluated. A 2019 clinical trial evaluated 750 ED patients with unhealthy alcohol use and randomly assigned them to receive either a computer-delivered BNI, therapist-delivered BNI with computer guidance, or enhanced usual care. The main outcome was alcohol use at 3, 6, and 12 months. Moderation of the intervention effect was also tested by gender, age, and severity of alcohol disorder. Overall, there was no difference in the main effects of either computer-delivered or therapist-delivered BNI compared to enhanced usual care. However, the therapist-delivered BNI group was more effective among patients with moderate to severe drinking patterns, while the computer-delivered BNI was more effective among younger participants [106]. Other benefits to computer-delivered SBIRT include its use in resource-limited EDs. There is also a reduction in time burden for care providers, enhanced fidelity of intervention delivery, and the potential for multilingual administration [86, 107, 108]. Overall, alcohol ED SBIRT represents a critical opportunity to identify patients with untreated AUD, particularly those who may not be seeking treatment. Once identified, these patients can receive a brief intervention or be linked to specialized treatment. Without this service, this precious opportunity is missed. Furthermore, both the NIAAA and Public Health Task Force recommend screening for unhealthy alcohol use; there appears to be no harm to the patients in doing so [109, 110].

Box 9.2 Modes of ED SBIRT for Alcohol Use Disorder

- Face-to-face physician/nurse interaction
- Specialty-trained paraprofessionals
- Computerized interaction
- Computerized and human interaction
- Smartphone-based interaction

Potential Value of ED-Based Alcohol SBIRT for Alcohol-Related Cancers

The ED serves a unique opportunity to detect unhealthy alcohol use and render services to those who present with concerns related to at-risk and hazardous alcohol use. In addition to decreasing use, ED-based SBIRT has shown some promise in reducing alcohol-related consequences such as MVCs [101, 103, 104, 111]. However, to date, there have been no studies that evaluate the effect of ED SBIRT on alcohol-attributable cancers. Existing evidence shows that alcohol use has a strong link to several types of cancers including head and neck, liver, GI tract, and breast [55, 57, 60, 62, 63, 72–74, 112]. By decreasing alcohol use, ED SBIRT has the potential to reduce exposure to alcohol (i.e., physiologically) and the risks of developing alcohol-attributable malignancy and other diseases associated with it, such as cirrhosis. Previous evidence has also shown that ED SBIRT can increase treatment access, particularly for those with alcohol dependence and AUD. A 2015 systematic review found that 7 out of 15 studies evaluated whether or not participants pursued treatment. Four studies compared the referral to treatment rates in the group that received BNI to the control group. One study showed a higher referral to treatment rate, in favor of the group that received BNI [113].

Recognition and treatment of severe AUD and its sequelae in the ED are also important among those with terminally ill disease such as advanced-stage cancer and liver cirrhosis. Alcohol dependency affects up to 28% of palliative care inpatients [114]. As high as 87% of patients with severe AUD receiving palliative care would not have been diagnosed had they not been screened [115]. ED clinicians should consider ongoing or worsening AUD in their differential diagnosis, particularly when evaluating patients with advanced-stage cancer. They should also consider identifying what appears to be signs and symptoms of acute alcohol withdrawal albeit in a less familiar context. Although evidence of the management of alcohol dependency among terminally ill patients is limited, ED clinicians should be proactive in recognizing and treating symptoms of acute alcohol withdrawal in this population. Low-dose benzodiazepines, such as lorazepam, are recommended with careful attention to those with liver impairment. Terminally ill patients who are interested in receiving detoxification are most appropriate for referral to the inpatient setting [116]. Alcohol ED SBIRT may also provide additional benefits in identifying unhealthy alcohol use in patients who have either received a new diagnosis of cancer or may be terminally ill.

Conclusion

EDs across the world diagnose and treat acute conditions related to unhealthy alcohol use such as MVCs and more chronic conditions such as liver cirrhosis and breast cancer. Thus, the ED is the ideal setting to identify patients with unhealthy alcohol use and motivate them to pursue treatment using SBIRT. It has shown promise in reducing alcohol consumption and alcohol-related injuries. By reducing alcohol consumption, ED SBIRT has the potential to reduce the risk of developing alcohol-attributable cancers as well. Tobacco and alcohol ED SBIRT, when used in conjunction, have the potential to have synergistic effects in reducing the overall burden of cancer [117]. However, additional research is needed to evaluate the effects of alcohol SBIRT in the ED on alcohol-attributable cancer.

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Ionizing Radiation

10

Richard T. Griffey

Case Study

A 28-year-old female with Crohn's disease presents with diffuse abdominal pain and low-grade fevers. She has had small-volume blood-tinged loose stools but no melena or vomiting. She was diagnosed with Crohn's disease at age 21 and has had several abdominopelvic CTs for staging and acute evaluations. She feels this may be a typical Crohn's flare but can't be sure. Knowing that as a young female at risk for repeat and multiple imaging with CT, which compounds an increased risk for luminal malignancies from her disease alone, the emergency physician discusses her care with her gastroenterologist and opts for imaging with magnetic resonance enterography (MRE) and admission, avoiding further ionizing radiation for non-obstructive symptoms.

Introduction

CT Is a Transformative Tool in Medicine

Computed tomography (CT) has numerous benefits that impact emergency care, including, but not limited to, decreasing negative appendectomy [1–5] and exploratory laparotomy rates, decreasing the need for hospitalization [6], allowing for safe discharge after exclusion of coronary disease [7], increasing provider [8] and patient [9, 10] confidence in diagnoses, and possibly even decreasing mortality [11] and increasing life expectancy [12]. Indeed, CT is fast, easy to obtain, relatively inexpensive, widely available, and highly sensitive, resulting in relatively low radiation exposure for the benefits obtained. The benefits of a CT *with appropriate indications* far outweigh the risks.

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The Explosion in CT Utilization

In light of this, it is perhaps not surprising that CT use has skyrocketed over the last two decades, with a growth rate of 14% per year for about a 12-year period [13]. In 1981, 3 million CTs were performed, increasing to over 67 million exams by 2006 (Fig. 10.1) [14]. One in ten Americans undergoes a CT scan every year, and many undergo more than one [15].

Increasing awareness about cumulative radiation in addition to other policies and guidelines may have contributed to a plateauing of CT imaging rates observed in the years 2008–2010 onward [16, 17]. Though this trend is true for overall CT rates, utilization in the ED has continued to increase [18]. It is estimated that one in seven ED patients undergoes CT and that 25% of CTs in the USA are performed in the ED [7]. In one study, 70% of the nearly one million non-elderly adults underwent at least one imaging study that included ionizing radiation, resulting in mean effective doses that nearly doubled the cumulative radiation expected from natural sources alone [19]. Similar patterns of CT use have been observed in pediatric populations as well, though more so in non-pediatric EDs [20, 21].

CT Contribution to Cumulative Radiation

Because of the much higher exposures that are imparted by CT when compared to radiographs, discussion of this modality drives the discussion about concerns over cumulative radiation exposure as well as costs [22]. Though by volume, radiographs comprise the majority of imaging studies, on a population basis, these account for a relatively small amount of cumulative radiation exposure [23]. Interventional diagnostic studies and therapeutic procedures, such as thallium scans and radiotherapy, can impart much higher radiation doses than CT but are not as commonly performed. In 2006, CT comprised about 17% of imaging procedures but was the source for over half the medical radiation dose in the USA (Fig. 10.2) [1]. The delayed nature of the carcinogenic effects

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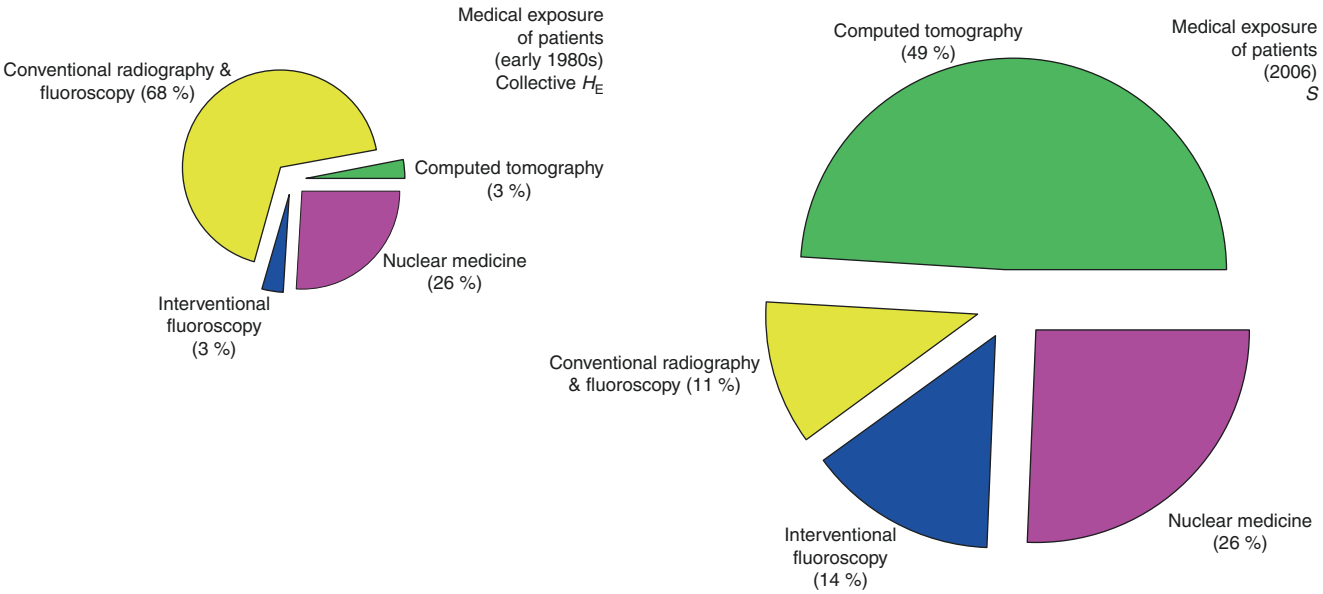

Fig. 10.1 Growth of CT from 1980 to 2006 as a contributor to cumulative radiation exposure. (From the National Council on Radiation Protection and Measurements, https://ncrponline.org/publications/, with permission)

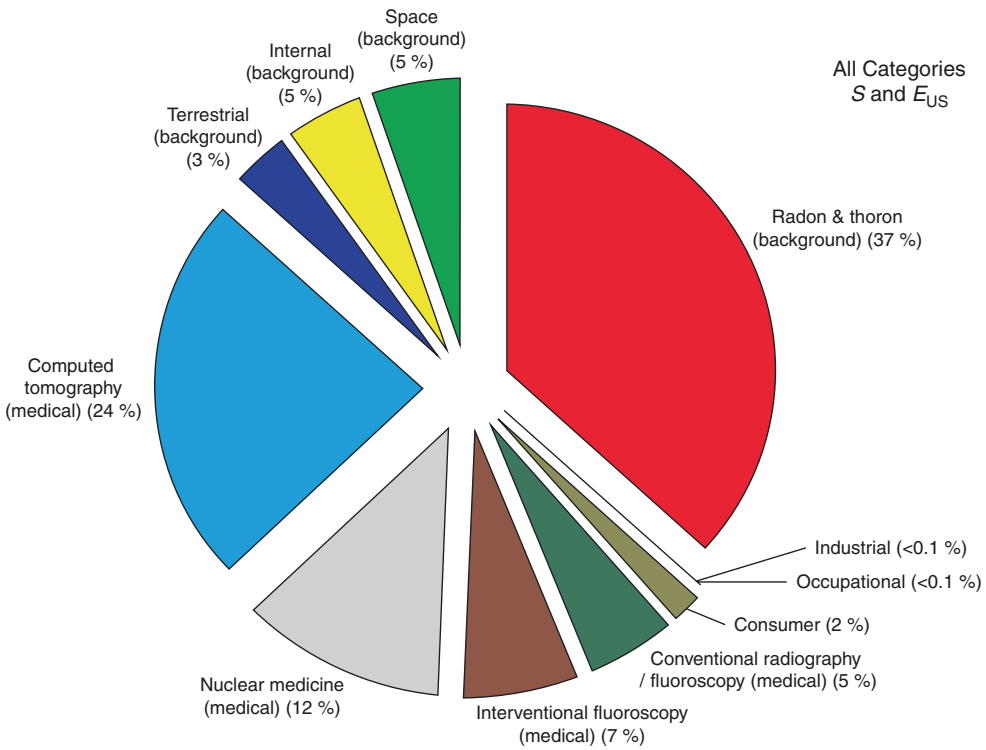

Fig. 10.2 CT accounts for over half of the cumulative radiation exposure from medical imaging. (From the National Council on Radiation Protection and Measurements, https://ncrponline.org/publications/, with permission)

of radiation exposure makes overutilization an insidious problem that fails to signal the usual alarms among patients or providers. Of concern, cumulative radiation from diagnostic imaging is projected to account for up to 5% of future cancers in the USA [15, 24, 25].

Reasons for Increased CT Utilization

Many reasons for the observed increases have been proposed, including but not limited to an aging population, the wide availability of CT, the replacement of older (X-rays)

with newer technology (CT), its speed and ease to obtain, concerns about malpractice and other factors, and for reasons that are surely multifactorial [18]. With hospital crowding, time pressures, the need to make decisions based on limited information, and a mandate to never miss life-threatening disease, the ED is fraught with the potential for error. This generally leads to a bias toward testing, including advanced imaging. It is important to appreciate that the increases in CT imaging in the ED have occurred in the context of a significant shift in the USA in the setting in which acute care is provided. The ED now accounts for nearly a third of the 354 million annual acute care visits in the USA, practically all acute care provided after hours and on weekends, more acute care for the uninsured than in all other settings combined, and nearly 50% of hospital admissions in the USA [26, 27]. To some degree, this shift in location of care explains some of the increases in volume of imaging performed in this setting, though early studies demonstrated that increases in CT utilization outpaced increases in ED visits [28]. Studies demonstrate that increased CT utilization far exceeds the amounts expected by replacement of technology [29] and that changes in tort law have had mixed findings as relates to CT utilization [30, 31].

Patterns of Repeat/Multiple CT Imaging in the ED

Though head and abdominopelvic CTs are the most commonly performed studies in the ED, it is known that certain indications for CT (e.g., kidney stones, suspected pulmonary embolus) predominate among patients who are repeatedly or multiply imaged [25, 32, 33]. It has been observed that significant proportions of CTs performed are unnecessary and/or could be replaced with other imaging modalities that do not impart radiation [34–37]. Studies identifying patients who are heavily imaged at a given point in time find that these patients tend to have multiple imaging generally and patients heavily imaged in the ED are also highly imaged in settings outside the ED [32, 33, 38].

Radiation and Its Effects

Radiation is the passage of an electromagnetic wave through space. At one end of the electromagnetic spectrum, lower-frequency and lower-energy waves, including radio waves, microwaves, infrared, visible and ultraviolet light, as well as ultrasound, comprise *non-ionizing radiation*. At the other end of the spectrum, the higher-energy, higher-frequency waves, including X-rays and gamma rays, are considered *ionizing radiation*. X-rays are produced when electrons are emitted from electron clouds as a result of electron excitation. Gamma rays are emitted from unstable nuclei as part of radioactive decay. Radiation is considered ionizing if it is of high enough energy to remove electrons from an atom. This is the basis for ionizing radiation causing cellular injury at the atomic and molecular level.

A displaced electron can cause direct injury if it hits and damages a strand of DNA or can indirectly damage DNA if the electron reacts with water, causing a hydroxyl radical that then interacts with DNA. When just a single strand of DNA is damaged, the cell is usually able to repair this, but when both strands are damaged, an abnormal reconnection of strands can occur, which is believed to account for the negative effects of radiation in humans. This may include a rejoining of strands incorrectly, leading to cell death or rejoining as a symmetrical translocation. This can result in oncogene expression during division and subsequent development of a malignancy or abnormal division in the gonads, potentially leading to hereditary disorders [39].

Deterministic Versus Stochastic Effects of Ionizing Radiation

At high doses, high-energy radiation causes direct cellular injury, resulting in what are called *deterministic effects*. These effects are dose related, occurring at threshold levels of radiation to cause sufficient cellular death within a tissue that then results in functional impairment of that organ or tissue (Fig. 10.3). Deterministic effects are discrete and specific, occurring within specific time frames following exposure. These effects are typically due to single large overdoses of radiation. Some examples include:

- Skin erythema, necrosis, and sloughing
- Cataract formation
- Sterility
- Radiation illness (GI tract, bone marrow, CNS)
- IUGR, teratogenesis, and fetal death

By comparison, so-called stochastic effects of radiation are due to DNA mutations whose effects become apparent after cell division. By definition, these are random, not guaranteed to occur, and they develop in an unclear time frame. Stochastic effect occurrence is thought to follow a linear, no-threshold (LNT) exposure where cumulative low doses result in increasing risk, not requiring some threshold level in order to cause these effects.

Organ	Effects	Thresholds (Sv)	
		Single absorption (Sv)	Prolonged absorption (Sv-year)
testis	permanent infertility	3.5 - 6.0	2
ovary	permanent infertility	2.5 - 6.0	> 0.2
lens	cataract	5.0	> 0.15
bone marrow	Blood forming deficiency	0.5	> 0.4

Fig. 10.3 Examples of deterministic effects of ionizing radiation. (From ICRP, 1991. 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Ann. ICRP 21 (1–3), with permission)

The Link Between Low-Dose Ionizing Radiation and Cancer

Without the benefit of direct observation to quantify amounts, considerable debate has existed about the nature of radiation exposure and the relationship to cancer. Questions about the relationship between radiation and cancer include whether cancer due to radiation results only from discrete exposures to some threshold amount, or whether the risk of cancer due to low levels of radiation increases in a linear (or other) fashion. Studies exploring this relationship have been based largely on data from observed vs. expected solid and liquid cancer rates among those in the blast zones of Hiroshima and Nagasaki, approximately 2000–3000 yards from ground zero receiving radiation in the 5–100 mSv range. Among 93,000 survivors followed over 55 years, 31,650 received a dose of 5–100 mSv. 44% of leukemia and 8% of solid tumor cases were attributable to radiation [40, 41]. Studies among survivors of the Chernobyl nuclear accident have also established the role of radiation as a precursor to malignancy. Other studies report increased all-cause mortality (primarily due to dose-related increases of cancer mortality) of nuclear workers related to cumulative low-dose exposure [42] and both projected cancers [43] and effects on cognition among infants exposed to low-dose radiation [44, 45]. In 2005, the US National Research Council's Seventh Biologic Effects of Ionizing Radiation Conference (BEIR VII) adopted the most widely used risk model for the effects of low levels of ionizing radiation [46]. The BEIR VII model, accepted by the International Commission on Radiological Protection and the UN Scientific Committee on the Effects of Atomic Radiation, holds that the risk of cancer from cumulative low-level radiation proceeds in a linear, no-threshold fashion so that low levels of radiation are cumulative and do not require a threshold level to increase the risk of cancer (Fig. 10.4)

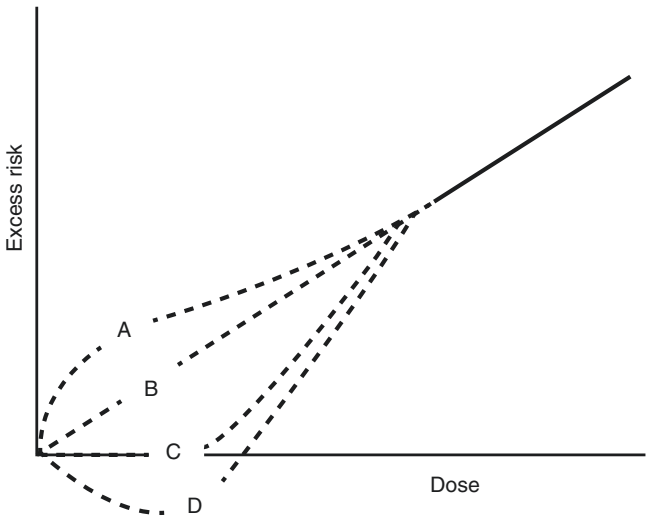

Fig. 10.4 Possible dose response curves for cancer induction at low doses. (**a**) Supralinear, (**b**) LNT (linear non-threshold), (**c**) threshold, (**d**) hermetic. Summing up the epidemiological data and biological findings, we are still unsure about the shape of the dose response curve in the low-dose range. While several dose response curves are possible as illustrated in the figure, the LNT model is usually adopted as a best estimate for low-dose risk. (From Anzai et al. [47], with permission Editorial Secretariat for JCBN)

[47]. Further, this risk model states that a 10 mSv exposure increases the risk of cancer by approximately 1/1000. In the USA, where the lifetime risk of cancer is approximately 42%, this means very crudely that a cumulative 10 mSv exposure increases this risk to 42.1%. Approximately half of cancers are fatal, and so by this risk model, a 10 mSv exposure translates to a risk of fatal cancer of approximately 1/2000 (Fig. 10.5) [46]. This model remains highly controversial, with major bodies, including the French Academy of Sciences, the American Nuclear Society, and the National Academy of Medicine suggesting that this model overesti-

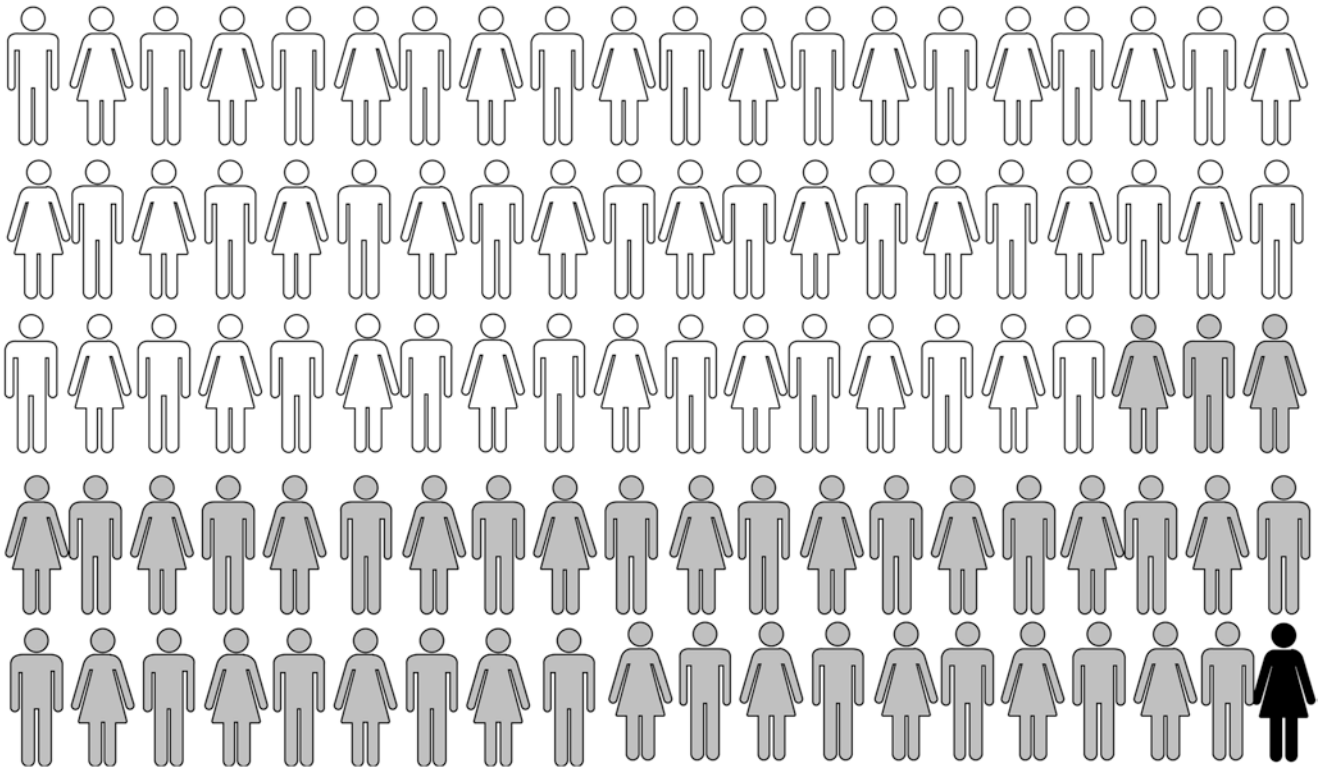

Fig. 10.5 In a lifetime, approximately 42 (solid circles) of 100 people will be diagnosed with cancer from causes unrelated to radiation. The calculation in this report suggests approximately 1 cancer in 100 people could result from a single exposure 100 mSv of low-LET radiation [46]

mates risk. It is important to appreciate that though this remains controversial, it is nonetheless the most widely accepted risk model. It is important to recognize that this model is unadjusted for gender and age at exposure. The American Association of Physicists in Medicine considers a cumulative dose in excess of 100 mSv to be of concern. The quantity of radiation that is considered to be "low dose" is generally in the range of 5–100 mSv.

Who Is Most at Risk?

It is known that age at exposure and gender are modifiers of risk. Women are scanned more frequently and are more sensitive to the effects of radiation, primarily due to increased radiosensitivity of female gonadal tissues [25]. Children have both a longer lag time to develop mutations or for mutations to result in malignancies, as well as increased radiosensitivity that declines with age [24]. However, recent models suggest that this decrease continues until middle age but that then cancer risks may then increase in a U-shaped distribution [15]. An additional risk factor is high cumulative radiation exposure due to multiple imaging. Certain conditions are known to be at increased risk for multiple imaging [32, 33, 48–53] including but not limited to inflammatory bowel disease (IBD) [51–55], kidney stones [20, 56, 57], and shunted hydrocephalus. This leads, in some patients, to very high cumulative doses and increases in lifetime attributable risk (LAR) of cancer. Patients who already have cancer may be at increased risk to develop second malignancies due to radiation. This is documented for radiotherapy, particularly for the lung, esophagus, luminal cancers [58], sarcoma, and breast cancer [59–61]. Cumulative low-dose radiation could represent another potential source of risk.

Measures of Radiation

There are many different units of radiation in use, and these can be difficult to remember for those who do not use them regularly. Measures of radiation relate to different aspects of radiation: exposure, absorption, biological effects, and for comparing effects and values of different exposures.

- *Exposure* to radiation can be measured in roentgens [R]. Exposure is the strength of a radiation field at some point in the air.
- *Absorption* is entry of radiation into body tissues and is measured in rads where 1 rad = 100 ergs/g or the International System of Units (SI) version and grays (Gy). A gray is defined as the absorption of 1 J (joule) of energy by 1 kg (kilogram) of matter. One gray = 100 rad.

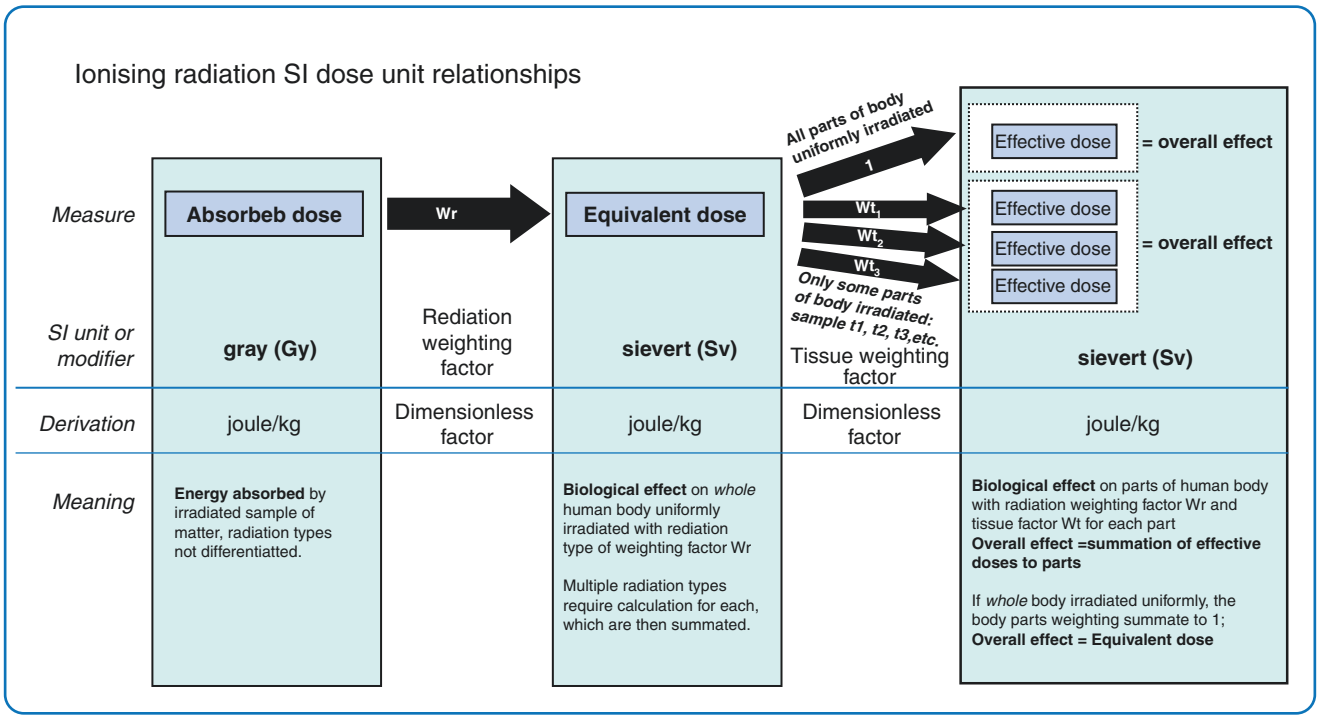

Fig. 10.6 Units and naming conventions for ionizing radiation. (From https://commons.wikimedia.org/wiki/File:SI_Radiation_dose_units.png with permission. Accessed: 8 Jul 2020 Courtesy of Doug Sim CC By-SA 3.0)

Absorbed dose is therefore expressed as a concentration, not an absolute amount. Absorption depends on the strength of the radiation, the distance from the source, and the duration of the exposure.

- The *biological effects* of absorbed radiation are measured in rems or sieverts (Sv), which is the SI unit.
- Important but sometimes confusing concept that is widely used and that can be somewhat controversial is that of *effective dose* (Fig. 10.6). This relates absorbed dose and biological effects. Effective dose is also used in comparing cancer risks and is not a dose but is rather a concept to reflect the risk of cancer from an exposure reflected over age and gender. It is expressed in millisieverts. Effective dose is determined by taking the sum of organ or tissue doses, multiplying these by the respective tissue weighting factors, based on an assumed uniform, whole body exposure. Because it is an average, unadjusted for age and gender, and mathematically derived using a standard body, it is not a true reflection of risk for an individual (Table 10.1).

Dose Estimates

Common units in estimating radiation dose include CT dose index (CTDI) and dose length product (DLP). Most current CT scanners generate these data based on the information provided in determining the protocol used, and these metrics can be reported with interpretations or in other lags. Reporting of CTDI and DLP may soon be required for all scans. CTDI can be thought of as the amount of radiation dose imparted in a single axial CT "slice" through the body with associated scatter and is measured by radiation detectors in a standardized acrylic "phantom" designed to detect doses to specific organs. Different variants of this measure exist, but the volume CTDI is most commonly used, measuring the amount of radiation delivered to the scan volume of a standardized phantom. DLP is the slice thickness multiplied by the number of slices acquired or length of the body scanned. When considering doses of radiation provided by a scanner, it should be remembered that these are not direct measurements for the patient on the gantry, but rather are estimates based on the protocol used as determined by detection in phantoms. In addition to age and gender, weight or body habitus also impacts the absorbed dose.

Efforts to Reduce Radiation and Optimize Imaging

Technological Improvements

At its most basic, CT is an X-ray tube that rotates around a patient. The X-rays passing through the patient are attenuated differently by different body tissues resulting in the detection of a pattern of photons by the detector opposite the tube. As a patient passes through the scanner, it acquires numerous "pic-

Table 10.1 Mean effective dose (mSv) for the 20 selected examinations[a]

Category	Examination	ICRP 60			IRCP 103			Sources for comparison	
		Mean	Min–Max	SD	Mean	Min–Max	SD	Mettler et al. [62]	DDM2 [63]
Computed tomography	Abdomen	8.1	5.1–11.7	2.0	6.8	5.6–8	1.2	8.0	11.3
	Chest	6.7	4.4–11.8	2.1	7.0	4.6–10.1	1.7	7.0	6.6
	Head	1.8	1.4–2.6	0.4	1.7	0.9–2.6	0.5	2.0	1.9
	Neck	3.2	1.8–6.0	1.3	3.0	1.7–5.8	1.9	3.0	2.5
	Pelvis	8.3	4.0–11.9	2.4	7.4	5.7–9.9	2.2	6.0	7.3
	Spine	10.3	4.0–16.7	5.3	7.0	1–12	0.0	6.0	7.7
	Trunk	12.2	6.7–15.8	3.3	12.3	10–16	2.0	–	14.8
Interventional cardiology	PCTA	19.5	7.4–48.6	15.1	7.2	–	–	15.0	15.2
Plain radiography	Abdomen	0.92	0.21–2.1	0.6	0.5	0.14–0.75	0.25	0.7	0.9
	Cervical spine	0.08	0.02–0.18	0.06	0.05	0.01–0.11	0.05	0.20	0.19
	Chest/thorax	0.07	0.01–0.14	0.04	0.05	0.01–0.07	0.02	0.02	0.10
	Lumbar spine	1.2	0.2–1.9	0.6	0.80	0.2–1.5	0.70	1.5	1.2
	Mammography	0.33	0.26–0.46	0.11	0.64	–	–	0.40	0.27
	Pelvis and hip	0.90	0.45–1.82	0.47	0.37	0.09–0.66	0.24	0.60	0.71
	Thoracic spine	0.60	0.23–1.22	0.43	0.50	0.1–1.2	0.40	1.00	0.64
Fluoroscopy	Ba enema	5.8	3.0–8.25	2.4	2.9	2.2–3.5	0.90	8.0	8.5
	Ba follow	3.5	1.2–7.7	3.7	1.3	1.2–1.3	0.10	5.0	7.3
	Ba meal	3.6	1.5–4.93	1.5	4.5	–		6.0	6.2
	Cardiac angiography	9.3	3.3–22.3	6.4	3.1	–		7.0	7.7
	Urogram	3.5	2.3–6.5	2.0	2.1	–		3.0	2.9

From Vilar-Palop et al. [64], with permission CC by 3.0
Note: Min, max, and standard deviation are shown only when more than one value was found
DDM2 Dose Datamed 2, *PCTA* percutaneous transluminal coronary angioplasty, *Ba* barium
[a]According to the two different sets of the International Commission on Radiological Protection values used (ICRP 60 from 1990 and ICRP1 03 from 2007) and the values of two sources for comparison

tures" in a 360-degree helical fashion that are then mathematically computed and joined to create an image that can be reconstructed in three dimensions. A number of technological improvements can greatly reduce dose per study:

- Standardizing the doses and protocols of CT studies so that for a given patient and a given study, the same dose is delivered. One study of four hospitals in the SF area found that for the same CT study in the same patient, doses varied by up to 13-fold. This sort of variability had significant implications as to projected cancer risk [65] and is unnecessary and wasteful.
- Optimizing aspects of data acquisition (e.g., speed with which the table passes through the scanner, length of body scanned, pitch at which patient passes through the scanner, minimizing amount of overlapped areas occurring due to the helical nature of the scan) may help reduce exposure.
- New detector technology, increasing detector number, and dual source imaging also offer the potential for lower doses [66].
- Accepting more noise in images where high resolution is unnecessary, such as for detecting ureteral stones, can decrease the radiation associated with this CT [67].
- Minimizing multiphase scanning, where patients are scanned, for example, first without, then again with, a contrast agent.
- Modulating tube current, where the amperage from the X-ray tube of a CT scanner is modified as it spins around the patient on the gantry such that a sufficient higher amperage is used in the plane in which the patient is wider and a lower mA setting is less used in the plane in which the patient is thinner.
- Use of shields, such as breast shields, may reduce dose to sensitive tissues. However, these also have limitations and can introduce noise and artifacts.
- Other technical features such as iterative reconstruction can provide high-quality images by eliminating sources of noise, for example, in the reconstruction of the data into images.

Though technological solutions hold promise to minimize the dose per scan, the biggest payoff in terms of radiation and certainly with respect to costs associated with imaging may come at the point of order entry and optimizing ordering to scan those who need it and avoid scanning those who do not. Changing provider behavior is difficult to do, however, as a number of different efforts have demonstrated.

Provider and Patient Awareness

Numerous studies have demonstrated lack of physician awareness of the risks of imaging, disbelief in risks of cancer related to radiation from imaging, and poor performance in estimating risks and equivalent doses of radiation between imaging modalities. This lack of knowledge crosses specialties, in some cases even including radiologists [68–73]. While these are mostly older studies that predate the current focus on this area, the few studies specific to EPs confirm these findings [68, 74, 75]. That said, it is not entirely clear what the right knowledge is: does it matter whether the EP knows the number of chest X-rays that are equivalent to an abdominal CT, or is it more important to know the increase in lifetime attributable risk imparted by an abdominal CT? What is the level of knowledge required for good decision-making? Raising awareness, though helpful, is likely insufficient on its own to make a difference. In one study, training house staff on radiation risks failed to change ordering behavior, though it made them more comfortable with discussing risks with patients [76].

Approaches to raising awareness have included a number of efforts providing information cards for physicians that outline radiation risk for patients, though studies of the effectiveness of these have not been published in the medical literature. One successful program in raising awareness is the Image Gently campaign, begun in 2007, and directed at improving the safety and effectiveness of the imaging of children. This includes "raising patient and provider awareness, providing education and advocacy on selection of appropriate imaging studies, and minimizing radiation dose to levels as low as reasonably achievable (ALARA) when imaging children" [77]. This successful campaign has subsequently led to the Image Wisely campaign directed at achieving similar goals for adults [78].

The few studies that have looked specifically at ED patient knowledge about radiation and their preferences found that patients generally prefer imaging and definitive diagnoses without concern for radiation or its risks [10, 11]. Studies among pediatric populations found that discussions of radiation risk with parents improved their understanding without causing them to decline necessary imaging studies [79]. In a survey of radiology department chairs at academic medical centers, two-thirds reported having guidelines at their institutions related to informed consent for non-emergent CT studies. And though informed decision-making related to imaging is recommended as a best practice [80, 81], only 15% included discussions about possible radiation risk of CT with their patients [82].

Clinical Decision Support

Appropriateness Criteria

A number of bodies have developed appropriateness criteria for imaging [83, 84], perhaps most notable of these is the American College of Radiology (ACR) Appropriateness Criteria, which consist of consensus-derived rankings of imaging studies and modalities for specific clinical indications for imaging. Particularly when radiologists are not available for consultation, rankings of appropriateness may help guide imaging selection and potentially curb overutilization. Providers board-certified in emergency medicine may find these criteria less useful in selecting appropriate imaging in the ED as this is part of their training and because daily practice and local resource availability inform selection of appropriate imaging modalities. In addition, rankings in the ACR Appropriateness Criteria are not impacted by the amount of radiation a study imparts, which is listed in a separate column called "relative radiation level."

Clinical Decision Rules

Clinical decision rules (CDRs) have been developed to help guide clinical practice in an evidence-based manner. Though this term is sometimes used casually, scientifically sound clinical decision rules require rigorous derivation and validation methods that are time-consuming and costly, requiring expertise to ensure their ultimate appropriate use. Moreover, it is unclear whether CDRs truly outperform clinical gestalt [85, 86]. CDRs relating to imaging have been developed to help determine whether patients require head CT imaging following minor traumatic brain injury, whether patients suspected for possible pulmonary embolus require chest CT, and whether patients with renal colic should undergo CT imaging [37, 87]. Even when a CDR is demonstrated to be effective, valid, and reliable, it is only useful if it is actually used. A number of studies describe how various imaging decision rules are underutilized [88–90]. One study estimated that use of a decision rule could prevent up to one-third of pulmonary embolus CTs [34].

Computerized Interventions

A common way to promote use of CDRs and appropriateness criteria is to embed them in computerized order entry systems. A limited number of studies have explored the

effectiveness of computerized decision support in the ED. There have been limited or no studies evaluating use of computerized decision support in providing information on the dose associated with commonly ordered CT studies, patients' individual CT study counts, associated cumulative radiation exposure, or lifetime attributable risks of cancer. One study described computer-assisted identification of patients who had accumulated certain threshold numbers of lifetime CTs, which then required a peer-to-peer conversation with a radiologist to proceed [91]. Though it has been proposed that patients might carry a card with them that specifies the amount of cumulative radiation they have had, it is unclear what providers should do with this information. One survey of EPs confirmed that though providers were interested in all forms of decision support and information described above, they were inadequately familiar with information on radiation dose to make use of such information clinically.

Shared Decision-Making with Patients

Emergency physicians want computerized tools to help guide decision-making and would like information that provides them with ways to discuss risks with their patients [75]. Data suggest that despite being recommended as best practice, discussions with patients regarding risks rarely occur [92]. A main limitation of shared decision-making as relates to CT imaging in the ED is that the decision to image is infrequently preference sensitive or at equipoise with some other diagnostic option. Conveyance of complex information is challenging enough in patients with adequate literacy and numeracy, let alone among those with lesser skills.

Quality Metrics and Regulatory Efforts

In addition to physician-initiated efforts to optimize imaging, a number of organizations and regulatory bodies have taken an interest in incentivizing improvements. Preauthorization is one approach taken by payers that has been successful in reducing imaging. However, it is frustrating for physicians to seek approval to care for their patients and would be highly impractical for use in the ED. Quality measures related to imaging have been advanced by various bodies, including proposals to report and track patient-specific dose information. Existing or proposed legislation in some states involves tracking CTDI and DLP. In addition, tracking and documentation of CTDI and DLP in each patient's record are required by the TJC for accreditation. Hospitals must compile and analyze data on patient CT radiation doses and compare these with external benchmarks when available.

The Centers for Medicare and Medicaid Services (CMS) have adopted imaging-related measures for the ED included as part of the Quality Payment Program. Other programs such as the Choosing Wisely campaign that focus on limiting avoidable imaging have also been championed in emergency medicine. One of these measures, directed at utilization of head CT in the ED for atraumatic headache, generated a fair amount of debate in the EM community. This measure, OP-15, was controversial because its derivation applied data obtained in a younger population to an older Medicare population, its exclusion criteria were felt to be insufficient, and it failed to include indications that were included in the American College of Emergency Physicians' clinical policies related to atraumatic headache and thus was felt to be invalid for public reporting. The Choosing Wisely initiative includes five recommendations directed at minimizing diagnostic radiation exposure: (1) avoiding head CT scans in patients with minor head injury who are at low risk based on validated decision rules; (2) avoiding head CT in asymptomatic adult patients with syncope, insignificant trauma, and a normal neurological evaluation; (3) avoiding CT pulmonary angiography for patients with low pretest probability of pulmonary embolism and either a negative Pulmonary Embolism Rule-Out Criteria (PERC) score or a negative D-dimer; (4) avoiding lumbar spine imaging for adults with non-traumatic back pain unless the patient has severe or progressive neurologic deficits or is suspected of having a serious underlying condition (such as vertebral infection, cauda equina syndrome, or cancer with bony metastasis); and (5) avoiding abdominopelvic CT in young otherwise healthy patients with known histories of kidney stones or ureterolithiasis, presenting with symptoms consistent with uncomplicated renal colic [93].

Summary

It is hard to imagine the practice of emergency medicine without the use of CT imaging. But it may be very important for the benefit of patients, to imagine practice with more judicious use of this tool, particularly for those at increased risk of cancer. Although the nature of the relationship of low-dose radiation and cancer remains controversial, it is accepted that radiation is a carcinogen and that high cumulative doses increase the risk of cancer. Awareness of the risks of CT imaging in young and female patients, particularly for those at repeat and multiple imaging, is a start toward appropriate use. A number of technological improvements are promising to reduce the dose per study. Decision support tools may be useful in helping risk-stratify patients to help in decision-making; however, more study is needed to evaluate their effectiveness. Quality measures and regulatory statutes related to tracking of cumulative doses may also help drive

improvement. Much work remains in order to make clinical use of this information. Finally, providing emergency physicians with options to CT imaging for high-risk patients, including alternate imaging modalities, is essential to help reduce utilization.

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Cervical Cancer Screening

11

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Case Study

A 16-year-old girl received one dose of the human papillomavirus (HPV) quadrivalent vaccine when she was 14. The girl and her mother have come for vaccination counseling. They want to know if she can finish the HPV vaccination series and how many doses she will need. The nonavalent vaccine is available. Which vaccine should she receive, and how many doses are necessary to complete the series?

The only vaccine available now in the United States is a nonavalent vaccine, so she should receive another one dose of nonavalent vaccine. In the settings where a quadrivalent vaccine is still available, the clinician would recommend that she should receive another one dose of quadrivalent vaccine.

If providers do not know or do not have available the HPV vaccine product previously administered or are in settings transitioning to the nonavalent vaccine, any available HPV vaccine product may be used to continue or complete the series for females for protection against HPV 16 and 18.

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Background

Cervical cancer is a leading cause of cancer death among women worldwide in spite of more than seven decades of effective prevention interventions. Cervical cancer is a preventable disease and its high mortality is unacceptable. In recognition of the morbidity and mortality associated with this preventable disease, in May 2018 the WHO Director General announced a global call for action toward the elimination of cervical cancer [1].

There were an estimated 569,847 new cases and 311,365 deaths from cervical cancer in 2018, and cervical cancer ranks as the fourth most commonly diagnosed cancer among women worldwide [2, 3]. The majority of cervical cancer cases occur in low- and middle-income countries (LMICs), where cervical cancer is often the most frequent cancer and the leading cause of cancer death among women. The global disparities in incidence and mortality of cervical cancer is due in part to the vast disparities in access to, and availability of, effective screening programs, including treatment of women who have precancerous lesions. Regions with the highest cervical cancer incidence rates are sub-Saharan Africa, Micronesia and Melanesia, Southeast Asia, Latin America, and the Caribbean [2].

Cervical cancer is a preventable disease. Primary prevention is available using one of the three available vaccines. If administered prior to sexual debut and exposure to HPV, generally in early adolescence, these vaccines will prevent 70–90% of cervical cancers. Furthermore, effective screening methods exist, including cytology and HPV testing. It takes many years for invasive cancer to develop following detection of a demonstrated persistent HPV infection and cervical dysplasia; thus there are many opportunities to intervene and treat a woman with abnormal screening test results. The main purpose of cervical cancer screening is to identify women with abnormal cervical lesions and treat precancerous lesions to prevent the progression to invasive cervical cancer.

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Human Papillomavirus (HPV)

HPV is the most common sexually transmitted infection. Extensive evidence links HPV and development of cervical cancer, and virtually all cervical cancer is caused by persistent infection with high-risk HPV [4]. The average lifetime probability of acquiring HPV is 85% and 91% among women and men who have had at least one sexual partner, respectively. More than 80% of women and men acquire HPV by age 45 years [5]. The initial infection generally occurs during adolescence or early adulthood. Approximately 80% of individuals with HPV will clear the infection spontaneously within 18–24 months of infection [6]. In women with persistent HPV infection, 3–5% will develop significant preinvasive disease, and <1% will develop cancer [7]. HPV infection is also associated with other malignancies, including oropharyngeal, anal, penile, vulvar, and vaginal cancers [8]. Persistent infection with a high-risk HPV (hrHPV) type is required for the development of cervical cancer.

HPV is a double-stranded DNA virus. There are over 120 HPV types, and approximately 40 types are known to infect the anogenital tract [9]. The HPV type distribution varies by population and geographic region [10].

HPV types are grouped by the potential of the virus to cause malignancy. Low-risk (non-oncogenic) HPV types do not integrate into the host cell genome. They cause genital warts, and low-grade cervical dysplasia. HPV types 6 and 11 are associated with 90% of genital warts. High-risk (oncogenic) HPV types are associated with high-grade cervical dysplasia and invasive cancer and may also be associated with low-grade cervical dysplasia. HPV types 16 and 18 account for 70% of cervical cancers and 60% of high-grade cervical dysplasia [11]. The DNA of high-risk HPV integrates into the host cell genome and causes neoplastic cellular changes. In most women, the HPV infection is not persistent, the virus is cleared naturally, and the dysplasia regresses. In a small percentage of women, the infection is persistent, and the transformed cells can replicate and progress to cancer after several years [11–13].

Cervical Intraepithelial Neoplasia (CIN)

Cervical intraepithelial neoplasia (CIN) is a precancerous lesion of the cervical epithelium. It is a histologic diagnosis made from a cervical biopsy specimen. In the Bethesda system for reporting cervical cytologic diagnoses (cervical cytology), findings are described with the term "squamous intraepithelial lesion (SIL)" and histologic findings described with the term "cervical intraepithelial neoplasia (CIN)" [14]. More recently, the 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) Risk-Based Management Consensus Guidelines for abnormal cervical cancer screening tests and cancer precursors recommended histopathology reporting based on Lower Anogenital Squamous Terminology (LAST) group classification scheme. Per these guidelines, histologic high-grade squamous intraepithelial lesions (HSIL) should be classified with CIN 2 or CIN 3 qualifiers, i.e., HSIL (CIN 2) and HSIL (CIN 3) as outlined below [14, 15].

CIN is graded into three degrees of severity depending on the how much of the epithelial layer contains atypical cells. The terminology of CIN is shown in Table 11.1. CIN 1 frequently spontaneously regresses, often within 6–12 months [16]. CIN 2 remains reversible, with approximately 40% regressing spontaneously without treatment [17]. CIN 3, once called severe dysplasia and carcinoma in situ (CIS), is a precursor of invasive cancer. Approximately one-third of CIN 3 lesions may spontaneously regress. However, treatment is recommended for CIN 3 [15, 18].

Risk Factors

The lifetime risk of developing cervical cancer is 0.9% and 1.6% in high-income countries (HICs) and in LMICs, respectively [19]. The most frequent age at diagnosis in the United States is 35–44 years [20]. Women who are immunocompromised from any cause (e.g., genetic disease, HIV infection, immunosuppressive therapy) have a higher risk of developing a persistent HPV infection [21].

The primary risk factor for cervical cancer is persistent hrHPV infection. The cofactors associated with developing cervical cancer include immunosuppression, smoking, parity, increased number of sexual partners, and oral contraceptive use [22].

Prevention

Primary Prevention: HPV Vaccination HPV vaccines protect against acquiring HPV infection and the development of subsequent HPV-associated disease. Three different vaccines are currently commercially available worldwide, although not in all countries (Table 11.2) [23–26]. All three vaccines are prophylactic vaccines. Randomized clinical trials have demonstrated 93–98% efficacy in the prevention of cervical dysplasia associated with the HPV types contained in the vaccine [27–31]. Once exposed and infected with a specific hrHPV type, the vaccine is not effective in preventing disease against that type. The vaccine should be given prior to HPV exposure to be effective and protective. Currently, the only vaccine available in the United States is the nonavalent vaccine. The availability of vaccines varies in different countries and regions.

Table 11.1 Terminology of cervical intraepithelial neoplasia

Bethesda classification	Cytology	LSIL	HSIL	
System	Histology	CIN 1	CIN 2	CIN 3
LAST Terminology	Cytology	LSIL	HSIL	
	Histology	LSIL (CIN 1)	HSIL (CIN 2)	HSIL (CIN 3)
Previous terminology		Mild dysplasia	Moderate dysplasia	Severe dysplasia/carcinoma in situ

CIN Cervical intraepithelial neoplasia, *LAST* lower anogenital squamous terminology, *LSIL* low-grade squamous intraepithelial lesion, *HSIL* high-grade squamous intraepithelial lesion

Table 11.2 Comparison of HPV vaccines [23–26]

	Bivalent	Quadrivalent	Nonavalent
Brand name	Cervarix™	Gardasil™	Gardasil-9™
Protection	HPV 16/18	HPV 6/11/16/18	HPV 6/11/16/18/31/33/45/52/58
Cross-protection	HPV 31/33/45	HPV 31	No data
Adjuvant	ASO4	Aluminum hydroxyphosphate sulfate	Aluminum hydroxyphosphate sulfate

Recommendation The Advisory Committee on Immunization Practices (ACIP) recommends routine HPV vaccination for all girls and boys at 11–12 years, though children can receive vaccines as early as 9 years of age. Catch-up vaccination is recommended for females and males aged 13–26 years who have not received the vaccine or who have not completed the vaccination series. The US Food and Drug Administration (FDA) recently approved the use of Gardasil-9™ up to age 45 years [32], and the ACIP suggests shared clinical decision-making between patient and doctor when considering vaccination in this age group (26–45 years) [33].

Schedule and Doses

- Individuals starting the vaccination series before age 15: two doses (0, 6–12 months)
- Individuals starting the vaccination series at age 15 or older: three doses (0, 1–2 months, and 6 months).
- Immunocompromised individuals: three doses (0, 1–2 months, and 6 months), regardless of age

If the vaccination series is interrupted or not given as scheduled, the ACIP recommends resuming at any time without restarting the series, regardless of the gaps in the vaccination schedule.

Efficacy Six landmark phase III studies demonstrated that HPV vaccines are highly immunogenic and effective in preventing the main oncogenic types of HPV infections. The data were from three studies of the quadrivalent vaccine [27, 28, 34], two studies of the bivalent vaccine [29, 30], and one study of the nonavalent vaccine [31]. The vaccine induced antibodies in all vaccinated individuals, and antibody titers in vaccinated individuals were higher than those produced by natural infection. Clinical trials of all three types of vaccines demonstrated an excellent humoral response with seroconversion rates near 95%.

The most recent evidence of HPV vaccine effectiveness is from large systemic reviews and meta-analyses, including data from 1702 articles with 60 million individuals and up to 8 years of follow-up. The data show the impact of HPV vaccines on HPV infections, CIN 2+, and anogenital warts. Among girls aged 13–19 years, the prevalence of HPV 16 and 18 decreased by 83%, and the incidence of anogenital warts decreased by 67%. In women aged 20–24 years, the prevalence of HPV 16 and 18 decreased by 66%, and the incidence of anogenital warts decreased by 54%. The incidence of CIN 2+ decreased significantly 5–9 years after vaccination by an estimated 50% among girls aged 15–19 years and 30% among women aged 20–24 years. In male participants, the incidence of anogenital warts decreased by 48% and 32% among boys aged 15–19 years and men aged 20–24 years, respectively [35].

The duration of immunity is not yet known, and so it is unclear if protection is life-long or whether a booster dose will be required. Because the vaccines do not provide protection against all cancer-associated HPV types, routine cervical screening is still recommended, including routine screening in vaccinated women.

Safety All HPV vaccines are made from virus-like particles (VLPs), which mimic the capsid of the virus but contain no genetic material [36]. These VLPs are not infectious and cannot cause an HPV infection. Several large clinical trials have documented all HPV vaccines to be safe, with no risks of serious adverse events. In addition, the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety has stated that the benefit-risk profile is favorable [37].

Bivalent Vaccine Large placebo-controlled randomized trials data revealed the safety of the bivalent vaccine. There were no differences in serious adverse events between vaccine and placebo. In post-licensure data from the United States, there were 52 reports to the Vaccine Adverse Event Reporting System (VAERS) following administration of bivalent vaccine through September 2011, and 98% were considered nonserious [38].

Quadrivalent Vaccine The safety profile of the quadrivalent vaccine was evaluated in diverse populations of females from different resource settings in large licensing trials and post-licensure safety surveillance systems. Mild injection site reactions were the most commonly observed adverse events. The data showed that the vaccine is safe and well tolerated [27, 28].

There were 21,194 reports of adverse events following HPV immunization from 2006 to 2013, in which approximately 57 million doses of quadrivalent HPV vaccines were administered in the United States. Of reported adverse events, 92% were considered mild. Among serious events, headache, nausea, vomiting, fatigue, dizziness, syncope, and generalized weakness were the most frequently reported. There was no evidence of increased risk of Guillain-Barre syndrome compared with other vaccines [39].

Nonavalent Vaccine The nonavalent vaccine became available in 2014 and is currently the only vaccine used in the United States. There are less available post-licensure safety data of the nonavalent vaccine since it is relatively new. The overall safety profile appears similar to that of the quadrivalent vaccine with a slightly higher incidence of mild or moderate local reactions (pain, erythema, and swelling). The frequency of systemic adverse effects (e.g., headache, fever, nausea, dizziness) is similar to quadrivalent vaccines. Serious adverse effects occurred in less than 0.1% [40].

HPV Vaccination Challenges and Barriers In the United States, the uptake of HPV vaccination is relatively low, with only 50% of age-eligible children receiving the full series [41]. The acceptance of the vaccine in other high-income countries (HICs), e.g., Canada and Australia, is higher at approximately 70–80%, likely due to government-supported school-based programs [42–44]. The Global Alliance for Vaccination and Immunization (GAVI) has made the HPV vaccine available to low-income countries for US$4 to $5 per dose [45]. However, there are many remaining barriers limiting universal mass vaccination programs worldwide.

One of the barriers to HPV vaccination is cost, which is approximately $150 per dose in the United States. Significant progress has been made to improve the affordability of the HPV vaccine in LMICs through financing mechanisms, including the GAVI and the Pan American Health Organization (PAHO) revolving fund [46]. However, many LMICs are still ineligible for financial support offered through the GAVI.

In many countries, a government supported school-based vaccination approach serves as an effective method to deliver the vaccine to adolescents. If girls do not attend school, the primary health centers and clinics can reach girls who missed vaccination [47].

General public knowledge of the importance of HPV vaccination is poor universally. There is widespread misinformation about the vaccine and the safety of vaccination, and some parents have been reluctant to have their children vaccinated. This is true even among well-educated populations in countries with high-quality healthcare systems [48].

Secondary Prevention: Cervical Cancer Screening

Cervical cancer screening to detect precancerous lesions, or CIN, enables treatment of pre-invasive lesions prior to development of invasive cancer. Screening tools include cervical cytology (Pap test), HPV testing, or a combination of the two tests. Systematic reviews and meta-analyses show that screening is associated with a significantly decreased incidence and mortality of invasive cervical cancer. Previous cluster-randomized studies from India revealed that a single screening test in a lifetime among women age 30–59 years decreased the risk of developing cervical cancer (relative risk 0.56, 95% confidence interval 0.42–0.75) and mortality from cervical cancer (relative risk 0.65, 95% confidence interval 0.47–0.90) [49, 50]. In many LMICs, Pap and HPV testing are not available. In these low-resource settings, visual inspection with acetic acid (VIA) is used to identify precancerous lesions of the cervix.

Cervical Cytology Dr. Papanicolaou demonstrated in 1928 that cancer and its precursors could be identified by examining an adequately prepared and stained cellular sample scraped from the uterine cervix [51]. This method of screening for cervical cancer precursors was adopted in many HICs in the 1940s. Although cervical cytology has low sensitivity, regular and widespread screening with cervical cytology has reduced the incidence of cervical cancer by 50–70% over the past 60–70 years [52]. Invasive cancer takes 10–20 years to develop from persistent HPV infection and resultant dysplasia, so screening can be an effective prevention strategy. Generally, women who develop invasive cervical cancer are women who have never been screened, or have not been screened regularly, or women who were screened, had abnormal cervical cytology, but did not receive follow-up treatment.

The conventional Pap test is performed by scraping cervical cells using a spatula and endocervical brush and smearing the cells on a glass slide for later examination by a cytologist/pathologist. In many countries in recent years, this method has been replaced with a liquid-based approach where the cervical sample is placed in a liquid medium initially, and the cells are later examined microscopically. This method allows for better preservation of the cervical cells and a higher-quality microscopic examination. The liquid-based collection method allows for cytology and HPV testing from the same sample.

HPV Testing HPV testing is now part of the routine screening algorithm in the United States. Studies have demonstrated that HPV testing has much higher sensitivity in detecting CIN 2+ than cervical cytology (96% vs. 53%) with slightly lower specificity (91% vs. 96%) [53–55]. HPV DNA testing has been recommended in both high- and low-resource countries [56, 57]. While cervical cytology is still widely used in LMICs, co-testing (cervical cytology and high-risk HPV testing) is now also recommended.

Several studies have examined the effectiveness of cervical cancer screening with primary HPV testing alone. In a large randomized study in Canada, 19,009 women were screened with HPV testing vs. liquid-based cytology. The study demonstrated that a woman with a negative HPV test vs. negative cytology had a significantly lower likelihood of CIN 3 and cancer at 48 months [58]. The high sensitivity of HPV testing leads to a much higher negative predictive value, implying that the screening interval can be safely lengthened if HPV testing is used [55].

Guidelines for Screening The ASCCP guidelines recommend screening for cervical cancer between the ages of 21 and 65 [59]. Cervical cancer screening should not be performed in women younger than 21 years of age, regardless of the age of onset of sexual activity. The screening guidelines, stratified by age, are summarized in Table 11.3

The US Preventive Services Task Force (USPSTF) recommends the primary high-risk HPV screening test as an alternative screening in the United States for women age 30–65 years. The USPSTF recommends screening with cervical cytology alone every 3 years, high-risk HPV testing alone every 5 years, or co-testing every 5 years in this group of women [60].

Colposcopy Women with abnormal cytology may be examined with colposcopy. The colposcope is a low-power binocular microscope with a powerful light source that is used for examination of the cervix. Acetic acid (3 to 5%) is applied to the cervix during this examination to enhance the visualization of dysplastic lesions [61]. A colposcopist can identify lesions and tissue patterns associated with cervical dysplasia and determine whether a biopsy is indicated.

Treatment of CIN Observation is preferred to treatment for women with CIN 1 [62]. In general, women with CIN 2/3 are treated because of the higher risk of progression to invasive cancer. Treatment of women with CIN 2 or CIN 3 to remove abnormal areas of the cervix may be through ablation (with cryotherapy or thermal ablation) or excision of the precancerous area. Success rates of these treatments are greater than 90% in properly selected patients [62, 63]. Excisional

Table 11.3 The American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP) summary of recommendations [59]

Population	Recommended screening methods	Notes
<21 years	No screening	Regardless of the age of onset sexual activity
21–29 years	Cervical cytology every 3 years	No HPV testing
30–65 years	Co-testing with cervical cytology and HPV every 5 years (preferred) or cervical cytology alone every 3 years	
>65 years	Screening is not recommended for women with a history of negative screening	Negative prior screening is defined as 3 consecutive negative PAP tests or 2 consecutive negative HPV tests, provided there is no history of high-grade dysplasia (CIN 2/3) or cancer in the past 20 years. Women 65 years of age or older who have not had previous screening should undergo cervical cytology and HPV testing
After hysterectomy with removal of the cervix	No screening	Screening is not recommended for women who have had a hysterectomy with removal of the cervix and do not have a history of CIN 2+
HPV vaccinated	Same as unvaccinated women	

CIN Cervical intraepithelial neoplasia

procedures include loop electrosurgical excision procedure (LEEP), cold knife conization (CKC), and CO2 laser conization. The choice of treatment modality depends on the availability of equipment and experience and expertise of the clinicians. In the United States, excisional treatment is preferred to ablative treatment for histologic HSIL (CIN 2 or CIN 3) [15]. Excision is also recommended for adenocarcinoma in situ (AIS) [62]. For specific treatment details, ASCCP guidelines should be consulted, as recommendations can change.

Cervical Cancer Prevention in Low- and Middle-Income Countries (LMICs)

The majority of cervical cancer cases occur in low- and middle- income countries (LMICs), where cervical cancer is a leading cause of cancer among women. Moreover, the death rate of cervical cancer in LMICs is 18 times higher than in HICs [64].

Although the screening and diagnosis algorithms described above are effective, they are expensive and require high-level infrastructure and well-trained personnel. In low-resource settings, personnel and medical specialists to provide prevention, screening, and treatment services are lacking, and shortages of infrastructure and pathology services are common. In several LMICs there are no gynecologic oncologists and no formal training in gynecologic oncologic. The International Gynecologic Cancer Society (IGCS) provides a Gynecologic Oncologic Global Curriculum and Mentorship Program, a comprehensive 2-year education and training program to train gynecologists in gynecologic oncologic in countries with no formal training program in this specialty [65].

In many LMICs there are no organized, effective cervical cancer screening programs, and few women ever receive cervical cancer screening. Furthermore, many women with abnormal screening results may be lost to follow-up and fail to receive diagnostic and therapeutic care for precancerous lesions [66].

One approach to screening in low-resource settings is the one-visit screen-and-treat strategy employing visual inspection with acetic acid (VIA) and immediate treatment with ablation if VIA screening is positive. VIA is performed by applying acetic acid to the cervix. Precancerous lesions will turn white with the application of acetic acid, and the identified lesion can be removed through ablation. Both VIA and ablation therapy (cryotherapy or thermal ablation) can be performed by nurses or trained community health workers [56, 57]. In some studies, screening with VIA was shown to decrease cervical cancer mortality by more than 30% in unscreened communities in LMICs [67, 68]. WHO also recommends HPV DNA testing as a primary cervical screening option in LMICs [56, 57].

Cervical Cancer Prevention in the Emergency Department

The emergency department (ED) can serve as a valuable public health resource. In the United States, the ED provides medical care to an estimated 60 million women, and approximately 20% of adults visit the ED for medical services each year [69, 70]. For underserved populations and people who lack access to regular medical services, the ED may be the only place some individuals receive healthcare services [71, 72]. In particular, underserved, low-income women are at increased risk of developing cervical cancer due to a lack of access to regular cervical cancer screening. Visits to the ED present an opportunity to provide, refer, or counsel women for cervical cancer prevention and screening.

A previous retrospective cross-sectional study of a stratified random sampling weighted to represent more than 100,000 visits to 4600 EDs showed the estimated median ED waiting time to be 30 minutes. The study also revealed that the median ED length of visit was 4.3 hours for admitted patients and 2.3 hours for discharged patients [73]. Some hospitals use these wait times as an opportunity for patient education in preventive health. Some centers use medical students, nursing staff, or health advocates to provide education in the waiting room. Moreover, education offered in the waiting room can be shared with families or caregivers and all visitors [74, 75].

HPV Vaccination

Physician recommendation of the HPV vaccine is a strong predictor of HPV vaccination initiation [76]. Recommendation of HPV vaccine in the ED is a potential channel to improve vaccination rates among populations who do not have access to routine medical care.

A cross-sectional study assessed attitudes of emergency medicine physicians toward recommending the HPV vaccine in an ED setting. The study surveyed the willingness of physicians to recommend the vaccine and identified barriers to vaccination in the ED settings. Of 100 physicians, 9% stated they would not recommend the vaccine to patients in the ED. Twenty-four percent were neutral, and 67% would recommend the vaccine. The study revealed that a lack of proper reimbursement for vaccination was a significant barrier to immunization in this setting [77]. Support and encouragement of emergency medicine physicians to inquire about, and recommend, HPV vaccination could be a useful step to improve primary prevention of cervical cancer.

Screening

Self-sample HPV testing has been proposed as an alternative method for cervical cancer screening in several settings. Women insert a small brush into the vagina to collect cervical samples without requiring a clinician-provided speculum exam. Many studies have shown the advantage of self-sample HPV testing in increasing screening rates and coverage [78, 79]. A previous study evaluated an acceptability of self-sample HPV testing among medically underserved women visiting the ED and found that 85% of participants were willing to use this method for cervical cancer screening [80]. Although this collection method is not yet approved by the US FDA, self-sampling HPV testing could be a potential strategy to improve cervical cancer screening among high-risk women who do not attend regular screenings.

A pilot study conducted at an urban ED found that referral combined with text messages resulted in a 43% increased uptake of cervical cancer screening among nonadherent groups [81]. The ED is a potential resource for improving HPV vaccination rates and cervical cancer screening rates. Patients can benefit from education about vaccination and cervical cancer screening and can also receive a referral for screening during a visit to the ED.

Conclusion

Cervical cancer remains an important public health problem in many countries and regions, including underserved areas of the United States. It is a disease that is preventable with HPV vaccination, regular cervical cancer screening, and follow-up care. However, access to care is a significant barrier for underserved women. Research suggests that the ED has great potential to serve as a resource for cervical cancer prevention.

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Lung Cancer Screening

12

Marcelo Sandoval

Introduction

Lung cancer (LC) is the most common and fatal cancer worldwide; in the USA incidence is decreasing, but it remains the deadliest cancer. Patients with LC come to the emergency department (ED) for disease or treatment complications. New LC will be discovered in some, and those with lung cancer diagnosed in the ED are more likely to have advanced disease refractory to treatment. Lesions that are likely benign with a small chance of representing early cancer are sometimes found in the course of ED evaluation. The current standard of care is to refer these patients for follow-up as recommended by various guidelines.

The historically grim prognosis for LC highlights the need for early detection. Lung cancer screening (LCS) of high-risk asymptomatic individuals with low-dose computed tomography (LDCT) has been shown to reduce mortality by finding LC at earlier stages but at the cost of false positives that can lead to unnecessary distress, radiation exposure, and invasive procedures. As the evidence base for screening grew, steps to minimize false positives and unintentional harm have been taken. Currently only a fraction of eligible patients are screened even though the Centers for Medicare and Medicaid Services (CMS) approved LDCT screening for LC as a preventative health service at 100% coverage in 2015. Currently, many patients at high risk for LC are likely coming to the ED for other reasons. We will review current evidence regarding LCS benefits and harms, barriers to screening, and how the new field of oncologic emergency medicine may help meet currently unmet LCS needs.

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Case Studies

A 65-year-old woman presents with cough, chest pain, and shortness of breath. A CT pulmonary angiogram shows no evidence of pulmonary embolism; however, it reveals a left upper lobe infiltrate, left pleural effusion, enlarged hilar lymph nodes, and several lobulated lesions in the left lung of varying sizes; largest one is about 35 mm, in the area where her pneumonia is present. On further questioning she admits to weight loss and hemoptysis over the past 2 months. After full evaluation you judge she is stable to go home with oral antibiotics. However, you inform her that some of the findings on history and CT are highly suggestive of LC. "How can that be? I've never smoked in my life! What are my chances, doctor?" as she begins to cry. What can you tell her about how she might have developed this, and what is her prognosis?

A 45-year-old male with upper abdominal pain and vomiting and tenderness in the epigastrium (but no Murphy's or peritoneal signs) is found to have an elevated lipase, total and direct bilirubin, and alkaline phosphatase. He has a history of fatty food intolerance and denies drinking alcohol. CT abdomen confirms a dilated common bile duct and mild pancreatic inflammation due to a retained common bile duct gallstone. He feels much better after symptom relief and IV fluids. Given the absence of fever or WBC elevation, you decide to discharge him with GI follow-up the next day. Fifteen minutes later the radiologist calls you. "Hi there. I looked more closely, and he also has a right lower lobe lung nodule that's 10 mm in diameter, with subsolid/ground glass and part-solid features, minimal attenuation of surrounding structures, and no calcifications. I thought you should know." He hangs up and you ask yourself: "Hmm, do I even need to tell him about this? It doesn't sound so big and he has no chest symptoms. If it's nothing, I don't want to worry him. What should I do?"

A 65-year-old "frequent flyer" who you see several times a month for non-emergent problems approaches you. "Hey Doc. I just came by to tell you I just turned 65, and I actually

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got my Medicare card yesterday, so now I don't have to come see you so often anymore! Maybe you can tell me how to get my hernia fixed I've been putting off, and seeing somebody for my knee pains and back pains instead of having to come see you all the time?" You smile because you like this patient, and after seeing him so often over the years, you've actually developed a rapport with him. You know he needs primary care. If only he would stop smoking! You tried to enroll him in smoking cessation a few times, but he wasn't interested. He told you "I feel good, I want to enjoy my life, and so what's the point of quitting? If I get the big C, there's nothing they can do anyway. My friend started coughing last year, he went to the doctor, and they found it in his lung. Two months later he was dead." Is he right? You know LC is very bad, and almost no one gets diagnosed early enough for surgical resection. So is there any point in looking for trouble since he feels well and looks pretty good for someone his age?

Background

LC is the most common and fatal cancer worldwide with 2.1 million new cases and 1.8 million deaths recorded in 2018 [1, 2]. The USA will see 229,000 new cases in 2020 [3]. Prostate and breast cancer are more common in men and women, respectively, but LC will claim 136,000 Americans, more than colon, prostate, and breast combined [3]. The National Cancer Institute (NCI) estimated LC expenditure has risen to $14.2 billion in 2018. In terms of lost productivity, $36.1 billion dollars are lost per year due to LC, more than for any other cancer [4].

Cigarettes and smoke exposure account for 90% of LC [5–7]. Pre-existing lung disease such as COPD and pulmonary fibrosis increases cancer risk and mortality. Smokers with COPD die from LC more than smokers without COPD [8, 9]. Cannabis-related risk is uncertain; pooled analysis in 2015 showed no specific links, but the investigators stated that they did not include enough heavy users [10]. More potent strains, medical and recreational use make further study warranted. Data on hookah smoking [5] and electronic cigarette-related LC risk [5, 7] are very sparse.

Never smokers (<100 cigarettes/lifetime) account for 15–25% of LC. Very common among Asian women [11, 12], it is rising in the USA [13] and affects women more than men for reasons that include lifestyle, genetic, and hormonal differences [14–16].

Environmental risk factors include uranium-derived radon in soil, homes [17], air pollution [18–21], and indoor coal burning [22]. Occupational risks include asbestos, arsenic, beryllium, cadmium, chromium, diesel fumes, nickel, and silica [5, 7, 11, 23]. Other known risk factors are age, HIV and family history, *Mycobacterium tuberculosis*, human papillomavirus, low socioeconomic status (SES), and Black, non-Hispanic White, or Native American status [5, 7, 11, 23].

Epidemiology and High-Risk Populations

Lung cancer occurs decades after smoking, so population-wide changes in incidence (new cases per 100,000 per year) and mortality (deaths per 100,000 per year) also lag by decades behind changes in smoking rates. Africa has the lowest rates of smoking [24], but use is increasing as disposable income grows [25]. Smoking peaked earliest among males (1970s) and females (1990s) in the USA, UK, Canada, and Australia; because men and women have been smoking less for decades, LC incidence and mortality have been declining for years in these countries [6, 7, 23, 26]. Higher-income northwestern European, South American, and Asian populations are experiencing more recent declines in incidence and mortality among males, due to decreases in male smoking over the last two decades [23]. At the same time, women's mortality is rising due to prior increases in smoking [6]. In low- and middle-income populations of southeast Europe, Asia, and South America, LC is rising sharply in men, less so in women, accounting for the recent global increases in cancer [6, 7, 26]. Air pollution also contributes to these rising rates, especially in China and Russia [27]. Among women, incidence and mortality rates have been declining in North America, Western Europe, Australia, and East Asia but remain the highest worldwide in these places [7, 28]. On a positive note, the World Health Organization's (WHO) Cancer Mortality Database showed tobacco cessation in North America, Europe, and South America has led to decreases in LC incidence and mortality in those under age 50 [29].

In the USA, despite incidence and mortality declines in both men and women, certain populations remain at high risk. 2019 American Cancer Society statistics show that Black Americans have long had the highest incidence and mortality of all ethnic/racial groups, despite declines in smoking among Black teens since the 1970s [30]. Incidence and mortality in Black individuals are followed closely by non-Hispanic Whites and Native Americans [31]; each group has about approximately 60–65 per 100,000 incidences and 35–45 per 100,000 mortalities. Black American male LC incidence (85.4) and mortality (63.9) are much higher than Black women (49.2 and 33.3, respectively). Men account for most of the burden among non-Hispanic whites and Native Americans as well [31]. Lower socioeconomic status [32] and education level also predict increased incidence and mortality [7]. A LC mortality belt across rural counties in Oklahoma, Arkansas, southern Missouri, southern Illinois, Kentucky, Tennessee, southern Ohio, West Virginia, and western Virginia is highly correlated with poverty, unemployment, lack of health insurance, obesity, and low air quality [21], as well as increased rates of smoking and decreased surgical treatment of stage I disease [33]. Asian and Hispanic Americans of both genders have the least incidence and mortality [6, 7, 31], and a 2019 meta-analysis showed that being

female (any group), Hispanic, or Asian American predicted increased survival from LC [34].

Others at risk for LC are lesbian, gay, bisexual, and transgender (LGBT) people; the disabled; mentally ill individuals; and low pay grade military personnel, due to disproportionate rates of smoking [35].

Pathology, Prognosis, and Treatment

80% of LCs are non-small cell (NSCLC), and 15% are small cell LCs (SCLCs); other carcinoid/neuroendocrine tumors account for the remainder [36–38].

The most common NSCLC is small-airway adenocarcinoma followed by central large-airway-based squamous cell carcinoma (SCC), which is almost always associated with smoking [39]. Traditionally, NSCLC referred to both as treatment was similar. However, since 2015 WHO guidelines emphasize biomarkers for individualized treatment with targeted and immunotherapy regimens [38, 40] making differentiation more important. In the early stage, both are amenable to resection.

Since the 1990s, adenocarcinoma is increasing, due to filtered cigarettes (allowing small carcinogens to penetrate deeper into the airways), while decreases in smoking have reduced SCC [23]. "Never smoker" LC is usually adenocarcinoma and is more common in women [15].

SCLC, also associated with smoking, is highly aggressive and classified as limited and extensive, with 20–25% 5-year survival and 10% 2-year survival, respectively [41]. There is hope combinations of chemotherapy and immunotherapy can improve this [42].

Early diagnosis and surgical cure has long been key to best prognosis [43–45], with stage I 5-year survival rates of 45–79% [46–48]. Efforts to improve outcomes from curative surgery have focused on techniques such as video-assisted thoracic surgery lobectomy (VATS), sublobar resection (SLR) [48], prognostic markers [49], and pre-surgical adjunctive treatments with immunotherapy [50]. For advanced LC, prognosis has changed little even with newer treatments [51, 52]. According to the NCI Surveillance, Epidemiology, and End Results Program (SEER), 5-year survival with localized disease is about 59% but only 5.8% in distant metastatic disease. Unfortunately, only 17% present with localized disease [3].

Lung Cancer in the Emergency Department

Data from the Nationwide Emergency Department Sample (NEDS) showed that of nearly 5 million US cancer-related ED visits in 2012, 10.3% were by known LC patients [53]. These patients most frequently went to EDs for pneumonia, COPD, and respiratory failure with 67% of visits resulting in admission. In a 2019 prospective observational cohort study of 1075 ED cancer patients, of whom 139 (12.9%) were diagnosed with LC, the most common symptoms were abdominal pain, fever, breathing abnormalities, nausea/vomiting, and throat/chest pain [54]. Major symptoms leading to ICU admission and short-term mortality were shortness of breath and altered mental status [55].

Diagnosis of cancer in the ED is summarized in a 2017 review by Zhou. Such patients are less likely to be curable, less likely to survive at 1 year, 3 months, and 1 month compared to those diagnosed electively, even when adjusting for staging [56]. It is relatively uncommon that emergency physicians expect to diagnose LC in a patient with cardiopulmonary symptoms. Serious illnesses such as pulmonary emboli, pericardial tamponade, acute coronary syndromes, pulmonary edema, anaphylaxis, pneumothorax, pneumonia, COPD exacerbations, and asthma are more commonly expected [57], and, of course, COPD and cardiovascular disease frequently co-exist with LC [58]. Common symptoms leading to LC diagnoses in the ED include cough, shortness of breath, chest pain, and/or hemoptysis [58–64]. Hemoptysis is the most predictive symptom [62–64], even more so if associated with cough, dyspnea, and weight loss [62].

A 2012 Michigan study compared patients diagnosed with LC in the ED to those diagnosed in other settings and found that ED patients had more co-morbidities, were older, more often female, more likely to be Black and more likely to present in advanced stages [65]. The authors noted the need for increased ED smoking cessation and cancer screening awareness.

Urban Black and Hispanic patients face disparities in health care, will go to the ED, and have worse outcomes for many conditions, including cancer [66]. In rural America, White individuals have twice the mortality from LC than their urban counterparts, even with similar staging distributions [33].

ED Imaging and Lung Cancer

Chest X-ray (CXR) has long been used for ED chest complaints [67, 68]. Since the late 1990s, however, computed tomography (CT) has replaced CXR for diagnosis of pulmonary emboli [69, 70], aortic dissection [71], coronary disease [72], and some pneumonias [73, 74] as it is more sensitive and more often changes management [73]. ED CT scanning also discovers more masses [75–77] and nodules [78, 79] than does plain CXR.

Lung masses (>30 mm) [80] are likely malignant; thus prompt referral to a pulmonologist is recommended. Other CT findings highly suggestive of cancer include pleural effusion, pleural nodules, enlarged hilar or tracheal nodes, endo-

bronchial lesions, post-obstructive pneumonia, spiculated or lobular borders, presence of a solid component within a ground glass lesion, and growth on serial imaging [81].

Nodules are rounded or irregular opacities (<30 mm) [80]. Attenuation can be solid (opaque) or subsolid, which can further be classified as ground glass (hazy) or part-solid (mixed features) [80]. Solid nodules are less likely to be malignant, especially if calcified or <6 mm in size, unless they are new or growing. Subsolid nodules are also unlikely to be malignant if smaller than 6 mm. Factors that increase the likelihood of malignancy include size >15 mm, spiculation, lobulation, upper lobe location, presence of COPD or pulmonary fibrosis, and a history of cancer or growth. Multiple (two to four) nodules are more likely malignant, but five or greater are less likely (unless there is history of cancer). The Fleischner Society makes recommendations for follow-up of incidental nodules found on CT. Unfortunately, discovery of these incidental nodules often happens after the patient has left the ED [82, 83], at which point the ED has responsibility for notifying the patient. Follow-up recommendations may vary from none to 3–12 months later, depending on the size, consistency, rate of growth, and patient factors. These guidelines do not apply to nodules found on CT screening for cancer (see Lung-RADS® below) or if the patient is < age 35 or immunocompromised or has a history of cancer [84]. For incidental nodules found in the ED, use of Fleischner Society Guidelines decreases the rate of follow-up scans and invasive procedures [85].

Lung Cancer Prevention

Smoking bans and cessation decrease LC incidence rates in a predictable fashion [86]. Cessation before age 40 reduces smoking-related mortality by 90%. Smoking cessation efforts in ED are fully discussed in another chapter of this book.

Fine particulate matter air pollution (PM2.5) is increasingly recognized as a risk factor for LC, disproportionately in the South and Midwest, among Black individuals and those living in socioeconomically deprived areas. Much of the risk associated with fine particulates occurs below current Environmental Protection Agency (EPA) standards for PM2.5, suggesting the need to reassess current clean air standards in the USA [87].

Although home radon testing is recommended by the CDC and EPA, it is infrequently performed as no state currently requires home testing. Some states mandate radon testing in public buildings or schools. Efforts to increase low testing rates include novel approaches such as smartphone apps [88]. Targeted public health efforts to increase radon testing in areas (Kentucky) where both smoking rates and radon levels are high [89] may be particularly effective given the known synergy of radon and smoking in causing LC.

Lung Cancer Screening with Chest X-Ray and the Problem of Overdiagnosis

LC screening (LCS) attempts early detection before symptoms appear, thus improving prognosis. The NCI-sponsored 1986 Mayo Lung Project randomized 2 groups of approximately 4600 male smokers to screening CXRs and sputum cytology every 4 months for 6 years against standard care (recommended annual CXR and sputum cytology). Twice as many early cancers were found, more surgery was done, and 5-year LC-specific survival was superior in the screening group; however, there was no benefit in overall mortality over 6 years [90]. Other contemporaneous NCI trials at Memorial Sloan Kettering [44] and Johns Hopkins [91] also confirmed lack of mortality benefit.

It is important to understand the difference between survival and mortality to interpret these seemingly contradictory results. Survival is measured as the percentage of those diagnosed with cancer alive after time, traditionally 5 years. It can be helpful when telling a patient how long they may have to live but is also used to identify improvements in treatment. Mortality is measured as those who die from a given disease per 100,000 of the general population per year. For a treatment to be deemed effective, both survival and mortality should improve [92]. Either can be increased by preventing death (screening or treatment) or preventing disease (smoking cessation), but survival can also be increased by diagnosing more people earlier, some of whom will not get sick. This phenomenon is intrinsic to cancer screening [93–95] and is termed overdiagnosis – i.e., finding early indolent (slowly progressive) cancers that will not progress to symptoms or death. The Mayo Lung Project found 206 cancers in the screening group and only 160 in the control group over 6 years; more early cancers were found by screening, but roughly equal numbers of late cancers were found in both groups [90]. If a randomized controlled trial is properly designed, and screening finds more early cancers, it should also find fewer late cancers (stage shift), keeping total incidence in the two groups approximately equal [94–96]. In addition, the smaller non-screening control group should eventually "catch up" to the screening group in numbers of cases, since two properly matched cohorts should have the same incidence of cancer over time. Too few subjects or too short a study period will not allow a stage shift or catch-up to be detected.

Technology that increases early detection will increase incidence (by finding more fledgling cases) and will also appear to improve survival because some of these will be slow-growing lesions that are not destined to harm over the follow-up period. Mortality, a static measure of deaths per year, is not affected by increases in detection of new cases, so it is not subject to overdiagnosis [92]. Over time, a relative reduction in mortality between the two groups is the best way to see if there is benefit to the treatment or screening.

The initial Mayo mortality rate over 6 years was equal – 122 deaths in the screening group and 115 deaths in the control group; 3.2 vs. 3.0 (deaths per 1000 person-years). When follow-up extended to 16 more years, there were still more cancers (585 vs. 500) in the screening group, but no difference in mortality (4.4 vs. 3.9 death/person-years). This strongly suggests overdiagnosis of indolent lesions in the screening arm that never progressed because these cancers did not result in more deaths [97]. The price of overdiagnosis is inappropriate testing and treatment of these indolent cancers.

Overdiagnosis has been long recognized in prostate and breast cancer [98]. The existence of indolent LCs was known for some time from autopsy studies [99] but was thought to be uncommon because most people who developed LC died. Formerly, these indolent cancers were known as bronchoalveolar carcinoma (BAL) but since 2015 have been reclassified by WHO and the American Joint Committee on Cancer (AJCC) [40, 100]. These lesions appear as malignancies on radiography and biopsy, and as there are no metastases, they are usually resected. However on resection they are found to have a lepidic growth pattern and are termed adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA). Both are very slow growing with almost 100% 5-year survival after resection compared to only 67% with other types on adenocarcinoma. They are so indolent that they may never manifest before a patient dies for other reasons, but identifying these prior to resection is not yet routine [100]. NCI is sponsoring research in genomic and molecular techniques to detect them, allowing for less invasive treatment or surveillance leading to similar good outcomes [101]. Since the advent of CT scanning, there is evidence that this occurs more frequently than previously thought, in up to 18% of cancers detected using low-dose computed tomography (LDCT) [102, 103].

The abovementioned CXR studies may have been underpowered to determine whether screening might have a small mortality benefit. The 2011 Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial was designed to detect smaller differences in mortality, randomizing 155,000 healthy smoking and non-smoking volunteers to annual CXR screening vs. usual care for 3 years. There was no mortality benefit [104], thus putting the question of CXR screening to rest.

Computed Tomography (CT) for Lung Cancer Screening

In the 1970s and 1980s, the potential of CT scanning for LCS led to a 1998 Japanese study by Sone et al. [105] and the 1999 Early Lung Cancer Action Project (ELCAP) study by Henschke et al. [106]. Both studies used LDCT protocols which had been developed and studied by Naidich [107] and Kaneko [108] with lower radiation doses than standard high-resolution scanning. Both found LDCT was vastly superior to CXR in finding earlier and smaller cancers; however, potential overdiagnosis, unnecessary testing, and invasive procedures made the value of CT screening less clear [94, 95, 109]. In 2006, Henschke et al. published a larger international multi-center study (I-ELCAP) evaluating annual screening CTs of smokers and non-smokers with other LC risks and incorporating 10- rather than standard 5-year follow-up. 412 of 484 detected cancers were in clinical stage I, with 88% 10-year survival with treatment; 92% if surgery was done within 1 month. The study concluded that CT screening could detect curable LCs as evidenced by long-term follow-up results [110]. Once more, the problem of overdiagnosis was cited [111] and the possibility that early AIS could regress due to innate defense mechanisms [112]. Also, as a one-arm observational case series without a control group, there could be no conclusion that early detection decreases mortality, despite the impressive 10-year survival rate. A randomized controlled study comparing CT screening with standard care was sorely needed [112].

National Lung Screening Trial

With this background, the NCI-funded National Lung Screening Trial (NLST) was initiated in 2002. Over 2 years, 53,454 current or former smokers aged 55–74 with 30 pack-years of smoking were recruited; if not currently smoking, participants had quit less than 15 years before. The subjects were randomized to undergo either three annual screening CXRs or low-dose CTs, and LC incidence and mortality were recorded for a mean of 6.5 years. The results were published in 2011. For the first time, screening showed a relative mortality reduction of 20% for LC and 6.7% in all-cause mortality. Unlike the CXR studies, "stage shift" was seen, more stage I (50% vs. 31%) but less stage IV (22% vs. 36%) cancers. Three hundred fifty-six deaths from LC occurred (247 per 100,000 person-years) compared with 443 deaths (309 per 100,000 person-years) in the chest radiography group. The number needed to screen (NNS) to save one life was 320. This was a landmark study demonstrating mortality reduction with LCS for the first time [113].

However, there were several concerns. Silvestri [114] and Bach et al. [115] noted that ~25% of CTs each year found "positive" nodules of which 96% were ultimately benign. Most follow-up for the "positive" nodules was radiographic, but approximately 6% had invasive testing (73% negative malignancy rate), and 10% had surgery (21% negative for cancer). Six patients without cancer died within 60 days due to workups. Furthermore, the study had well-trained radiologists and surgeons (surgical death rate was only 1%, much

better than average), motivated volunteer subjects, mostly ex-smokers, and only 8% were over age 70. Hospitals with less compliant, older patients with more co-morbidities and less experienced physicians would likely have worse benefit and harm rates. Screening benefits could be offset by increased smoking in those who became anxious from false positive results or falsely reassured by negative ones. Increased radiation and reduced quality of life due to anxiety were also cited [114, 115].

Overdiagnosis again became an issue. Finigan and Kern noted that of 119 additional cancers detected by CT, 75 were indolent bronchoalveolar carcinoma (BAL), now known as AIS and MIA [96]. Patz et al. analyzed NLST data and estimated an 18.5% overdiagnosis rate [102]. In 2013, the American Academy of Family Medicine (AAFP) concluded that insufficient evidence existed to recommend for or against LCS with low-dose CT [116].

The US Preventive Services Task Force (USPSTF) reported their assessment of LCS with low-dose CT in 2013. Humphrey et al. noted in a review written for the USPSTF that the NNS of 320 was better than those for mammography and sigmoidoscopy [117]. Because of concerns regarding overdiagnosis and harm, the Cancer Intervention and Surveillance Modeling Network (CISNET) developed screening simulation models incorporating age, frequency, and smoking history combinations predicting the most benefit for the least CT scans. The models predicted that by increasing age to 55–80 and keeping smoking requirements the same would result in superior outcomes than NLST criteria [118]. The USPSTF made a level B recommendation to Congress that all smokers aged 55–80 years and that have a 30 pack-year smoking history and currently smoke or quit within the past 15 years should get annual LDCT screening [119]; this led CMS (Centers for Medicare and Medicaid Services) to approve LCS as an annual preventative service benefit for all eligible Americans up to age 77 without copayment in 2015 [120].

There are strict requirements for federal LCS coverage and reimbursement [120, 121], including a documented shared decision-making conversation in the medical record that specifies the patient's eligibility by age and smoking history, the risks and harms of screening, and concurrent offers of smoking abstinence and cessation. LC CT screening programs must be accredited and use a central registry: the ACR Lung Cancer Screening Registry (LCSR), provided by the American College of Radiology [122]. In 2014 the ACR released Lung-RADS®, the Lung CT Screening Reporting & Data System [123] to better standardize reporting of findings among radiologists reading screening CT scans. Lung-RADS® increased nodule size threshold to 6 mm and incorporated other evidence-based criteria for nodule management. Applying the criteria to the NLST data, there was a 50–75% decrease in false positives which could lead to less invasive procedures [124]. Lung-RADS® is now the standardized method for radiologists to report on LCS nodules and make management recommendations. Version 1.1 was released in 2019 (Fig. 12.1).

Barriers to LDCT Screening

Jemal and Fedewa used the CDC National Health Interview Survey (NHIS) and found less than 4% of eligible Americans underwent LCS in 2015, and about 50% were uninsured or on Medicaid [125]. In comparison, screening rates among eligible candidates is 83% for Pap tests, 71.5% for mammography, and 62.4% for colorectal cancer screening tests [126].

Since 2012 the National Comprehensive Cancer Network (NCCN), comprised of 30 leading cancer centers dedicated to improving cancer care, has added a second group (group 2) to the population that should be eligible for LCS. NCCN consensus is that risk comparable to NLST criteria exists for patients age >50, 20+ pack-years of smoking, *and* one other risk factor (history of cancer, COPD/pulmonary fibrosis, family history of LC, radon exposure, or occupational exposure to carcinogens). Though initially a lower-level 2B recommendation in 2012 [127], the NCCN upgraded this to 2A in 2015 [128]. Pinsky had written in 2012 that strict adherence to NLST criteria would only find about 27% of lung cancers [129]; if criteria was expanded to those age 50–79, and any smoking history (current or quit <15 years), almost 50% of cancers could be found, though there would be much higher NNS and possible harm. By 2015 he found that the risk of current smokers with 20–29 pack-years was equivalent to that of former smokers with 30 or more pack-years; more women and minorities would be eligible for screening if the smoking requirement was reduced [130]. NCCN has recognized these and other studies by continuing to recommend group 2 LCS in their 2020 guidelines; they do acknowledge "true risks and benefits of screening these group 2 individuals are uncertain" and state a PLCO risk score [131] may help select the most appropriate group 2 individuals for LCS [132]. Two studies at single centers compared LCS in NCCN group 1 and 2 patients and found 1–2% rates of new cancer in both, but neither could not comment on mortality due to short follow-up or small sample size [133, 134]. The American Association for Thoracic Surgery has adopted similar LCS guidelines, advocating NCCN group 2 patients should be eligible for screening. They also added another group: those who have a history of LC and have been disease-free for 4 years [135].

Barriers to LCS in patients are awareness, cost, fear of cancer diagnosis, stigma of smoking, and radiation fears. Providers' barriers include unfamiliarity, lack of prompt access to accurate smoking history, time constraints for

Lung-RADS® Version 1.1

Assessment Categories Release date: 2019

Category Descriptor	Lung-RADS Score	Findings	Management	Risk of Malignancy	Est. Population Prevalence
Incomplete	**0**	Prior chest CT examination(s) being located for comparison Part or all of lungs cannot be evaluated	Additional lung cancer screening CT imaged and/or comparison to prior chest CT examinations is needed	n/a	1%
Negative No nodules and definitely benign nodules	**1**	No lung nodules Nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules	Coutinue annual screening with LDCT in 12 months	< 1%	90%
Benign Appearance or Behavior Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	**2**	**Perifissural nodule(s)** (See Footnote 11) < 10 mm (524 mm^3) **Solid nodule(s):** < 6 mm (< 113 mm^3) new< 6 mm (< 34 mm^3) **Part solid nodule(s):** < 6 mm total diameter (< 113 mm^3) on baseline screening **Non solid nodule(s) (GGN):** < 30 mm (< 14137 mm^3) **OR** ≥ 30 mm (≥ 14137 mm^3) and unchanged or slowly growing **Category 3 or 4 nodules unchanged for ≥ 3 months**			
Probably Benign Probably Benign finding(s) - short term follow up suggested; includes noduless with a low likelihood of becoming a clinically active cancer	**3**	**Solid nodule(s):** ≥ 6 mm to < 8 mm (≥ 113 to < 268 mm^3) at baseline **OR** new 4 mm to < 6 mm (34 to < 113 mm^3) **Part solid nodule(s):** ≥ 6 mm total diameter (≥ 113 mm^3) with solid component < 6 mm (< 113 mm^3) **OR** new < 6 mm total diameter (< 113 mm^3) **Non solid nodule(s):** (GGN) ≥ 30 mm (≥ 14137 mm^3) on baseline CT or new	6 month LDCT	1-2%	5%
Suspicious Findings for which additional diagnostic testing is recommended	**4A**	**Solid nodule(s):** ≥ 8 to < 15 mm (≥ 268 to < 1767 mm^3) at baseline **OR** growing < 8 mm (< 268 mm^3) **OR** new 6 to < 8 mm (113 to < 268 mm^3) **Part solid nodule(s):** ≥ 6 mm (≥ 113 mm^3) with solid component ≥ 6 mm to < 8 mm (> 113 to < 268 mm^3) **OR** with a new or growing < 4 mm (< 34 mm^3) solid component **Endobronchial nodule**	3 month LDCT; PET/CT may be used when there is a ≥ 8 mm (≥ 268 mm^3) solid component	5-15%	2%
Very Suspicious Findings for which additional diagnostic testing and//or tissue sampling is recommended	**4B**	**Solid nodule(s):** ≥ 15 mm (≥ 1767 mm^3) **OR** new or growing, and ≥ 8 mm (≥ 268 mm^3) **Part solid nodule(s) with:** a solid component ≥ 8 mm (≥ 268 mm^3) **OR** a new or growing ≥ 4 mm (≥ 34 mm^3) solid component	Chest CT with or Without contrast, PET/CT and/or tissue sampling depending on the *probability of malignancy and comorbidities. PET/CT may be used when there is a ≥ 8 mm (≥ 268 mm^3) solid component. For new large nodules that develop on an annual repeat screening CT, a 1 month LDCT may be recommended to address potentially infectious or inflammatory conditions	> 15%	2%
	4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy			
Other Clinically Significant or Potentially Clinically Significant Findings (non lung cancer)	**S**	**Modifier - may add on to category 0-4 coding**	As appropriate to the specific finding	n/a	10%

IMPORTANT NOTES FOR USE:

1) Negative screen: does not mean that an individual does not have lung cancer
2) Size: To calculate nodule mean diameter, measure both the long and short axis to one decimal point, and report mean nodule diameter to one decimal point
3) Size Thesholds:apply to nodules at first detection, and that grow and reach a higher size category
4) Growth : an increase in size of > 1.5 mm (> $2mm^3$)
5) Exam Category : each exam should be coded 0-4 based on the nodules(s) with the highest degree of suspicion
6) Exam MOdifiers: S modifier may be added to the 0-4 category
7) Lung Cancer Diagnosis: Once a patient is diagnosed with lung cancer, further management (including additional imaging such as PET/CT) may be performed for purposes of lung cancer staging; this is no longer screening
8) Practice audit definitions: a negative screen is defined as categories 1 and 2; a positive screen is defined as categories 3 and 4
9) Category 4B Management: this is predicated on the probability of malignancy based on patient evaluation, patient preference and risk of malignancy; radiologists are encouraged to use the McWilliams et al assessment tool when making recommendations
10) Category 4X: nodules with additional imaging findings that increase the suspicion of lung cancer, such as spiculation, GGN that doubles in size in 1 year, enlarged lymph nodes etc
11) Solid nodules with smooth margins, an oval, lentiform or triangular shape, and maximum diameter less than 10 mm or 524 mm3 (perifissural nodules) should be classified as category 2
12) Category 3 and 4A nodules that are unchanged on interval CT should be coded as category 2, and individuals returned to screening in 12 months
13) LDCT: low dose chesr CT

***Additional resources available at - https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads**

***Link to Lung-RADS calculator - https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/**

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Fig. 12.1 Lung CT Screening Reporting & Data System (Lung-RADS®). Lung-RADS® v1.1 Assessment Categories (2019 Release) (Courtesy and with permission of the American College of Radiology, CC BY-ND 4.0)

required shared decision-making, lack of support by specialists, and skepticism about benefit [136, 137].

Racial barriers to LCS were summarized by Borondy Kitts in 2019. Black individuals have higher rates of cancer and death than Whites but may be less likely to qualify for LCS due to lower smoking rates. She called for CMS to approve NCCN group 2 criteria and expand LCS for Black Americans. To date, however, LCS of NCCN group 2 is not covered by CMS or private insurance. Education, socioeconomic status, lack of primary care, mistrust of providers, and providers' implicit bias are additional barriers to LCS uptake among Blacks [138].

Annangi showed Black Americans have rates of early-onset LC (age 45–54) 73% higher than Whites [139]. A review of NLST data by Balekian et al. demonstrated ethnic disparities in rates of curative surgery for stage I LC. Black men had a 61% rate of curative surgery for stage I, whereas White men and women and Black women underwent curative surgery in 90% of cases. The reasons for these disparities are unclear [140].

Geographically, the South has 40% of screening-eligible patients, but has the lowest density of ACR-designated screening centers, and a 3.5% screening rate. In contrast, the Northeast has the lowest eligible percentage (15.5%) but the highest density and screening rate (10.1%) [141].

23% of the screening-eligible candidates live in rural areas [141]; however, most screening centers are in metropolitan areas; 28% of eligible patients have to drive 30 minutes or more to reach a screening center [142].

LCS barriers in the community hospital setting include low rates of screening by poorer eligible patients in favor of inappropriate screening of ineligible but affluent people, poor adherence to Lung-RADS® follow-up recommendations, poor patient compliance with follow-up, and inaccurate smoking data [143].

Huo et al. compared CDC NHIS data from 2010 and 2015, finding a trend toward increased CT LCS by people ineligible for screening and raising concerns regarding overuse of the modality in some settings [144].

While gays, lesbians and bisexuals have higher ratios of smoking, and thus higher percentages who are screening-eligible, they receive LCS ratios rates similar to their heterosexual counterparts [145]. One report from Japan demonstrated that screening-eligible schizophrenics, despite higher smoking rates, are less likely to receive screening [146].

Radiation risk from medical procedures is the subject of another chapter in this book, but perceptions of radiation risk among patients and providers bear discussion. Ionizing radiation is typically quantified as effective dose measured in millisieverts (mSv). LDCT in NLST delivered a mean effective dose of 1.4 mSv [147]. For perspective, the background radiation effective dose is 3 mSv per year, while a coast to coast flight is 0.035 mSv [148]. One CXR = 0.1 mSv per exam; a standard chest CT = 8 mSv; positron emission tomographic (PET) scans = 14 mSv; and a CT angiogram for pulmonary embolism = 10 mSv [149]. Bach in 2012 pointed out that NLST could lead to 1 radiation-related cancer death per 2500 people screened due to cumulative follow-up CT and PET-CT doses of 8 mSv over 3 years [115]. McCunney calculated that doses to smokers in annual LCS programs for 30 years would exceed that of nuclear plant workers [150]. The risk of developing cancer from LDCT was studied by the investigators of the Italian COSMOS; in their group of 5200 receiving annual CTs for 10 years plus PET-CTs for positive nodules, 1.5 LCs and 2.4 cancers could have occurred. They calculated 1 radiation-induced cancer for every 108 LCs found, but younger women 50–55 had a higher risk of radiation-induced cancer than other groups. They noted that all scans (including follow-up) were performed using low-dose technique, unlike NLST. They stated that Lung-RADS® would further reduce radiation and that technology would reduce CT dose even more; thus radiation-associated toxicity could decrease in time [151].

Proposed Solutions to LCS Barriers

Solutions to improve rates of LCS include provider incentives, use of dedicated navigators for patients and providers, further identification of barriers, and obtaining more accurate smoking histories [136, 137, 143]. Solutions addressing mistrust of the medical system include campaigns to engage patients, using testimonial success stories, avoiding scare tactics, and recruiting trusted community providers (rather than screening program representatives) to invite candidates to screening [136–138]. Racial and socioeconomic disparity solutions include expanding screening to Black Americans using NCCN group 2 criteria [138], seeking funding for free CT screening programs, providing free transportation, mobile CT screening centers, scheduling screening on evenings and weekends to minimize lost time at work [137], and developing culturally tailored educational and outreach programs in collaboration with community health centers and leaders [138].

Successful implementation of LCS program in non-academic community centers was demonstrated in two recent studies. Over the first 5 years of a community-based LCS program, 1241 patients underwent screening for 1 round, and 29 cancers were found, 72% in stage I. There was a 21.3% Lung-RADS® "positive" CT rate, with 20% of these false positive. An unfavorable finding was low adherence (37%) to repeat scanning in those with a negative scan, leading to speculation that this first negative result may falsely reassure some participants [152]. In another larger study, 3400 patients in a large community hospital network were screened over several years, 500 (14.6%) had "positive" CT, and of these 111 had cancer (95 lung, 16 others). Of the 95

LCs, 67 were stage I or II and they reported a 2.3% surgical mortality rate. The program had an 83% adherence rate to repeat screening. Diagnostic and complication rates were comparable to NLST, contradicting the belief that NLST results could not be generalized to the community setting [153]. Future studies may influence the AAFP to change their stance on LCS.

Ultra-low-dose CT (ULDCT) is a newer modality that provides comparable resolution to LDCT, with even lower doses of radiation (~0.13 mSv) almost equivalent to 1 CXR [154]. It is expected that this form of CT scanning will replace LDCT over time, further reducing radiation risk.

Management of nodules found through LCS has evolved since NLST. Lung-RADS® criteria raised the positive nodule threshold to 6 mm on initial scan or 4 mm for new nodules on subsequent scans. Growth is defined as an increase of 1.5 mm in size. Criteria were designed to decrease unnecessary repeat CTs, PET scans, or biopsies.

It is possible to reduce the need for repeat CT scans of nodules found on LCS by using software to calculate volumetric size rather than linear diameter to more accurately assess growth and increasing the interval for subsequent scans after the first two annual rounds in those with negative results to 2 years. These ideas were incorporated into subsequent large randomized control trials [155].

The Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) Trial

The Dutch-Belgian NELSON study was initiated in 2003 and was designed to find a 25% reduction in mortality with 80% power over 10 years [156]. They recruited adults aged 50–75 with >15 cigarettes per day for >25 *years or* >10 cigarettes per day for >30 years, currently smoking or had quit <10 years previously. They were randomized to screening vs. standard care without screening. The protocol called for a baseline CT, subsequent scans at 1, 3, and 5.5 years and then follow-up for 10 years. The most obvious differences between NELSON and NLST were the lower age limit and less intense smoking history (mean 38 pack-years vs. 56 pack-years NLST) requirement. By including subjects with moderate risk, the investigators calculated that they be would be able to recruit the necessary number of people (16,000) to adequately power the study, as well as apply the results to a broader population [156].

The study used 16- and 64-detector MDCT scanners vs. four-detector scanners in NLST. Software allowed 3D volumetric rather than 2D linear measurements. Nodules would be classified as low, intermediate, or high risk based on size, newness, and other features. Low-risk nodules would be recorded and the patient would return for the next scheduled screening scan. High-risk nodules would be referred immediately to a pulmonologist for biopsy; if negative the patient would stay in the study for the next scheduled screening. Intermediate-sized nodules would receive a repeat CT after 1 ½ to 3 months per protocol to calculate growth by volume doubling time. Growth rates faster than specified cutoffs would be referred to a pulmonologist for further evaluation. If cancer was diagnosed, the patient would then leave the study. If negative, they would return for further screening rounds. NELSON 16-detector MDCTs emitted 2 mSv for all exams [157]. The protocol was designed to minimize repeat scanning of intermediate lesions to one CT, after which a decision to refer or not would be made.

The final results were published in *The New England Journal of Medicine* in 2020 [158]. After randomization of 13,195 men, 344 cancers in the screening group and 304 in controls were found. 203 of the 344 cancers in the screening group were actually detected by screening – 44 were diagnosed between screenings and 97 after cessation of screening. Almost 60% of cancers detected by screening were stage I vs. 14% in the control group. Mortality over 10 years was 24% lower in men and 33% lower in a separate analysis of women (only 2594 subjects were women, due to low smoking prevalence). Benefit was seen even with the longer 2-year intervals after the first two screenings, demonstrating that less frequent screening in those already proven "negative" twice was viable. Overdiagnosis was estimated at 10%, and the NNS to save one life was 132. They found that after the first round, approximately 20% of participants required a repeat CT within 3 months to assess intermediate nodules, similar to other studies. However, for rounds 2–4, only 1.9–6.7% required a short-term repeat CT, and over half of new nodules resolved. Only about 2% of the CTs were "positive" in each round, and about one-half of those had cancer, giving a false positive rate of about 1.2%. In NLST the false positive rate was almost 25%. All age and smoking sub-groups showed mortality benefit; examining only NLST-eligible NELSON patients, a trend towards mortality benefit exceeding NLST was seen. The *NEJM* editorial by Duffy stated: "With the NELSON results, the efficacy of low-dose CT screening for lung cancer is confirmed. Our job is no longer to assess whether low-dose CT screening for lung cancer works: it does. Our job is to identify the target population in which it will be acceptable and cost-effective" [159].

Future of Lung Cancer Screening

Of note, the authors of NLST published an extended 12-year update on their subjects in 2019. At 12 years there were 1701 LC cases in the LDCT arm vs. 1681 in the CXR arm, thus showing equal incidence due to catch-up. Stage shift was preserved, i.e., more stage I (39.6% vs. 27.5%) and less stage IV (27.5% vs. 35.5%), and was similar to the original.

Overdiagnosis was down to 3%. Relative reduction in LC mortality fell to 11% (previously 20%), and there was no benefit in all-cause mortality, which had been 6.7%. Likely long follow-up period in an older cohort allowed catch-up in mortality for other reasons. NNS remained stable at 303, which signified that the signal of LC deaths prevented by screening had lasted for a decade and was due to cure, not delay in death. The conclusion was that there was still benefit even more than a decade, further reinforcing the effectiveness of LCS.

The Microsimulation Screening Analysis Lung (MISCAN-Lung) model was used to project the ramifications of full-scale LCS, and it found that there would be less need for chemotherapy and radiotherapy but there would be major increase in demand for surgery above current capacity. Careful planning and increasing the number of thoracic surgeons as quickly as possible would be imperative [160].

There is likely benefit to screening patients who do not meet CMS criteria and defining this group is a current topic of debate. Some advocate criteria based on personal risk calculation [161], and others advocate selection of those who could live longer after screening [162].

Text messaging to increase colon, breast, and cervical cancer screening has had moderate success [163] and bears further study for LCS. There is currently a multi-center clinical trial randomizing LCS active smokers to three arms for smoking cessation: standard referral, digital-based education/reminders on phone, and computer and a tobacco treatment specialist/digital combination [164]. Creating similar clinical trials using electronic platforms for recruiting, educating, and reminding candidates of LCS may be viable.

The SARS-CoV-2 (COVID-19) pandemic has changed medical practice around the world and has affected LCS. In April 2020, the American College of Radiology and the American Thoracic Society jointly created expert consensus statements to delay the reassessment of incidental or LCS nodules with low/intermediate risk potential for at least 3–6 months and to delay LCS baseline exams for 3–6 months, to be re-examined as the situation unfolds. For high-risk nodules with 65–85% certainty of malignancy, PET-CT or biopsy to assess need for surgery or radiotherapy is recommended rather than proceeding directly to surgery as was recommended by prior guidelines. Only the highest-risk nodules with >85% certainty of malignancy, should proceed to empiric surgery or radiotherapy. The goal of the strategy was to decrease risk and conserving personal protective equipment (PPE) by reducing procedures [165]. Amit et al. wrote and editorial that questioned the postponement of LCS, pointing out that mortality for LC is higher than that for COVID-19 and warning of a "cancer boom" in the future. They advocate frequent reassessment of this policy, and upon reopening, using triage systems to prioritize those who might benefit the most. They also call for cross-disciplinary discussion, merging of programs and resources and collaboration to help decrease the coming backlog in a way that helps the most people for the lowest cost [166].

In these efforts, telemedicine can help to maintain social distancing while allowing shared decision-making sessions with a provider.

Health Economics

As stated previously, LC has very high costs in terms of expenditures and lost productivity [4]. Much of the cost occurs due to treatment and complications of late-stage disease. Cost-effectiveness studies are designed to convince insurers to pay for LCS by estimating the costs incurred for screening in return for quality life-years. A 2013 study found LCS was as cost-effective as cervical and colon screening and better than mammography, diabetes screening, HIV testing, cholesterol medication, and dialysis [167]. A 2019 CISNET computer modeling study compared cost-effectiveness and mortality benefits of LCS in NLST-, CMS-, and USPSTF-eligible groups and found the CMS criteria gave the best combination of cost-effectiveness, quality life-years, and mortality benefit [168]. Applying NLST criteria would cost less but have less benefit while USPTF criteria would give the most benefit but also be the most expensive. The cost to insurers of expanding screening to patients using NCCN or NELSON criteria was not estimated.

One of the centers using NCCN criteria to expand LCS reported on profitability analysis for the institution. They actually offered LCS CT for free, regardless of insurance status. As a result of this screening, 60 new patients entered their healthcare system, and profitability above the initial overhead was achieved after 2 years [169]. They also noted that 73% of the lesions found were stage I, and the cost of treatment was $10,000 to $20,000. Costs associated with treatment of stage III or IV LCs are $80,000 to $100,000. The argument that healthcare systems can profit from LCS may speed their dissemination.

Cancer Prevention and Screening in the ED

Smoking cessation counseling in the ED has been studied since the early 2000s and is discussed in detail elsewhere in this book. EDs have long been involved in public health initiatives such as accident prevention, domestic violence screening, and vaccinations, among others. The idea of using EDs to promote cancer prevention is also not new. A 1996 study screened 116 women for breast and 644 for cervical cancer in a busy New York City ED with an underserved population. Nine patients with cancers underwent treatment [170]. In 2006, Cummings et al. in Canada reported using ED surveys about cervical cancer screening and immunizations and finding 307 women overdue for Pap smears. One hundred fourteen were contacted in follow-up and 54

(47%) reported receiving an outpatient Pap smear. Four of the 54 had significant pathology requiring further intervention [171]. Zun and Downey in Chicago questioned ED patients (mainly Black and Hispanic) about colon, prostate, cervical, and breast cancer screenings; of the patients who accepted referrals, 33% (breast) to 53% (colon) had confirmed appointments on follow-up [172]. In contrast, a 2008 Boston-based survey conducted in three academic EDs found that most women and a majority of men were compliant with recommended cervical, breast, testicular, and prostate cancer screening compared to general population, regardless of race or ethnicity. This population was 65% non-Hispanic White and had higher average income than most urban ED populations [173]. A 2017 analysis of the National Health Interview Survey found that patients who used the ED for health care were far less likely to have had recommended cancer screening than those with a usual source of care [126]. An initiative to promote public health topics (not including cancer screening) in a busy Maryland ED used interactive computer kiosks, noting that self-selection of motivated individuals could potentially lead to more efficient delivery of health education and even follow-up without sacrificing ED time or staff [174].

Emergency medicine organizations such as the American College of Emergency Physicians, the Society for Academic Emergency Medicine, and the American Academy of Emergency Medicine all have sections and/or polices on public health, and SAEM has an interest group dedicated to oncologic emergencies.

Lung Cancer Screening in the ED: What Is Our Role?

General barriers to screening include poor access to health care, lack of awareness or skepticism by primary care providers about LCS, fears of radiation exposure, concerns about cost, concerns about adequate interpretation of LDCTs, concerns about unnecessary invasive procedures, and concerns about a positive diagnosis, to name a few. In addition, racial/ethnic minorities, rural residents, and sexual minorities who are at high risk but medically disenfranchised face additional barriers to this potentially lifesaving procedure.

EDs act as the nation's safety net and are integral to our healthcare system. Public health and cancer prevention initiatives are already part of our profession's infrastructure and mission. We could help to increase screening in different ways. Most EDs use electronic health record (EHR) systems that allow patients to be "flagged" for various conditions, including public health concerns. EHRs have been shown to improve colon and breast cancer screening rates in ambulatory settings [175]. It would not be difficult to adapt such tools to ED EHR systems to identify such patients when they present. The teachable moment during a health emergency is often mentioned and has been shown to increase patient's willingness to change behavior, particularly with regard to substance abuse [176, 177]. Existing ED smoking cessation programs are another avenue to recruit eligible patients as many of them are likely at higher risk for LC.

Education targeting high-risk patients as they come to EDs for any reason is a relatively low-cost opportunity to improve screening rates. Use of modern technology such as computer/kiosks or smartphones, texts, and social media platforms may help by giving patients preliminary information about LCS without need for a dedicated person to do so.

Navigators for LCS programs performing outreach and facilitation for patients and providers have had some success facilitating screening in other settings, and liaison between EDs and local LCS existing navigators may serve to increase recruitment without dedicating ED personnel to the task. Partnering of community hospitals or freestanding EDs in remote areas with distant LCS centers may be facilitated by the use of telemedicine, as this modality becomes more familiar.

Any initiative into public health and cancer screening by EDs will certainly require coordination between local and state government authorities, philanthropic programs, public health programs, large medical centers, and community stakeholders. Whatever solutions that EDs adopt should not detract real-time resources from the EDs' primary mission.

Shared Decision-Making

Ideally, the burden of formal shared decision-making conversations and documentation that are a CMS requirement for LCS reimbursement should be undertaken by primary care physicians, pulmonologists, or oncologists in the proper setting [178], rather than the ED. Even if not formally part of a referral network, any ED can direct eligible patients to publicly available decision aids regarding LCS to help patients with decision-making (Table 12.1).

Table 12.1 Online resources for lung cancer screening

Agency for Healthcare Research and Quality: https://effectivehealthcare.ahrq.gov/decision-aids/lung-cancer-screening/home.html
American Thoracic Society: https://www.thoracic.org/patients/patient-resources/resources/decision-aid-lcs.pdf
Brock University Lung Cancer Risk Calculators: https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/
CDC (Centers for Disease Control and Prevention): https://www.cdc.gov/cancer/lung/basic_info/screening.htm
MD Anderson Cancer Center: https://www.mdanderson.org/publications/oncolog/house-call%2D%2Dlung-cancer-screening.h12-1591413.html
NCI (National Cancer Institute): https://www.cancer.gov/types/lung/patient/lung-screening-pdq
Veterans Health Administration: https://www.prevention.va.gov/docs/LungCancerScreeningHandout.pdf

Table 12.2 Key points/pearls

Lung cancer in the USA is the costliest cancer in terms of productivity and lives lost
COPD and coronary disease often co-exist with lung cancer, and COPD increases lung cancer mortality
Never smoker's lung cancer (LC) incidence is rising, and patients tend to be women. In East Asia, women have very high incidence of never smoker lung cancer, likely due to genetic variation. Air pollution is another cause of never smoker cancer, as is radon, as well as many other environmental exposures and medical conditions
Black men have the highest incidence and mortality from lung cancer, but non-Hispanic White and Native American men also have very high risk and mortality; there is correlation with geography, poverty, low air quality, and poor access to medical care. Others at risk include LGBT, disabled individuals, and enlisted military personnel. ED diagnosis of LC is associated with poor outcome
Shortness of breath and altered mental status correlate with ICU admission and short-term death
Adenocarcinoma and squamous cell LC are curable with early detection and surgical treatment but have poor prognosis if not resectable. Small-cell lung cancer remains highly deadly, even if found early
Incidental CT masses >3 cm are likely malignant and should be referred for further diagnosis. In adults 35 and older, lesions <6 mm in diameter are very unlikely to be malignant, unless the patient has history of cancer and immunosuppression or the lesions have irregular or spiculated morphology or are in the upper lobe location. Multiple nodules (2–4) are more likely malignant, but 5 or greater are less likely (unless there is history of cancer). Radiologists use Fleischner Society Guidelines for follow-up recommendations of suspicious lesions as part of the reading
Lung cancer screening is recommended by most medical organizations and approved by CMS for active or former smokers 55–77, with 30 pack-years of smoking, and those who have quit less than 15 years ago
Another high-risk group are those age >50 with 20+ pack-years ***plus*** history of cancer, COPD/pulmonary fibrosis, family history of LC, radon exposure, or occupational carcinogen exposure
Only 4% of eligible patients receive lung cancer screening (LCS) despite the test's approval by Centers for Medicare and Medicaid Services (CMS)
Overdiagnosis and false positives can lead to unnecessary distress, radiation, and procedures, but decreasing unintentional harm has been a priority in LCS research
Radiation dose from LDCT is about 10 times that of CXR, and one-fifth the dose of standard chest CT. As technology and protocols advance, the dose may soon approach that of 1–2 CXRs
Emergency physicians and departments can help increase LCS by "flagging" eligible patients using electronic medical records and then working with local LCS programs approved by the American College of Radiology. Many of these are developing outreach and navigator programs to increase recruitment and may be able to provide education and logistical support to interested patients. Use of telemedicine, cell phone, and social media platforms can be integrated. Coordination with local and state government authorities, philanthropic programs, public health programs, large medical centers, and community stakeholders is essential to maximize effectiveness and minimize dilution of ED resources

Conclusion (Table 12.2)

LC is the deadliest of all cancers in the USA and across the world. Despite advances in treatment, later-stage disease remains highly fatal. Early diagnosis at an early localized stage is the best chance for cure, and mass screening that had been unsuccessfully attempted for decades is only recently possible with LDCT. The potential for saving lives and costs makes increased screening for early LC a public health priority. Increasing the numbers of eligible patients who undergo screening should be approached on many different fronts.

As the safety net for society, the ED should certainly be able to assist with recruitment and referral. Real-time use of LDCT in eligible patients where CT scanners are not otherwise available may be another avenue worth exploring. However, this would only work if there is coordination with LCS programs and treatment centers. Partnerships with local community resources, advocacy in government circles at the regional and state level, and recruitment of philanthropic support are likely keys to success.

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Colorectal Cancer Screening

13

Veronica Sikka, Raaj K. Popli, and Edward P. Cutolo Jr.

Case Study

Patient is a 68-year-old male presenting to the emergency department (ED) with hematemesis with a 30 pound unintentional weight loss in the last 2 months. His hemoglobin is 10 with associated lightheadedness. His previous hemoglobin last month was 14. He is also complaining of low back pain. He reports never having a colonoscopy.

Upon presentation, the patient is given IV fluids and an NG tube is placed. Additional labwork is pending. A CT of the abdomen reveals a large obstructing mass in the cecum with dilated small bowel. Multiple liver metastases are seen affecting most lobes as well as lytic lesions in the lumbar spine. What is this patient's prognosis?

If the patient had received his routine colonoscopy, this cancer could have been detected at the polyp stage. Treatment options include (1) resection of the primary lesion; (2) palliative radiotherapy to the vertebral metastasis; and/or (3) systemic chemotherapy with biological therapy. His expected prognosis is not promising with a median survival of 24 months with systemic treatment.

Background

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer in the United States and the third most common cause of death for both men and women after lung and prostate for men and lung and breast for women. The American Cancer Society estimates that in 2020, 104,610 people will be diagnosed with CRC and 53,200 people will die from the disease alone [1]. Fortunately, the incidence of CRC has declined steadily in recent years and is largely attributed to the detection and removal of precancerous polyps with CRC screening [2, 3].

Although the overall incidence is declining, incidence in patients under the age of 50 is still on the rise as screening is not as common [4]. Surgery is considered the first-line therapy for CRC and is generally elective. Chemotherapy and radiation are also treatment options in more advanced stages. Unfortunately, patients with CRC may present to the emergency department (ED) with complications such as perforation, hemorrhage, and obstruction, as well as general complications secondary to chemotherapy and radiation [5]. This chapter focuses on (1) the diagnosis of CRC in the ED and (2) the ED recognition and management of patients with CRC-related complications.

The lifetime risk of obtaining colorectal cancer is 1 in 23 (4.4%) for men and 1 in 25 (4.1%) for women, with a higher predominance in men compared to women. CRC incidence is 30% higher in men. Lifetime risk is similar in men and women despite higher incidences in men. This is attributed to higher life expectancies in women. In comparing 5-year age groups, the incidence rate almost doubles until age 50, after which it increases by approximately 30%. Interestingly, patients diagnosed with CRC are younger today than ever before. In the early 2000s, the median age at diagnosis was 72. Today it is 66 years old. This is due to an increase in CRC screening over the years [3, 6].

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Diagnosis of CRC

The diagnosis of CRC is not straightforward. First, the cancer can be discovered at any stage during progression, from asymptomatic cancer identified by screening through consultation with a general practitioner or gastroenterologist to presentation as a surgical emergency (usually with bowel obstruction or perforation) [7, 8]. If diagnosis is delayed and surgery is emergent or palliative in nature, it is associated with a substantially elevated risk of mortality [9], especially among the elderly [10]. However, if detected early, the 5-year survival rate is 90% while still localized (i.e., confined to the bowel wall), 68% for regional disease (i.e., lymph node involvement), and only 10% if distant metastases are present [1, 11, 12].

Risk for CRC is increased by genetic mutations (i.e., familial adenomatous polyposis, Lynch syndrome, juvenile polyposis, and Peutz-Jeghers syndrome), personal history (i.e., irritable bowel syndrome, Crohn's disease, and ulcerative colitis), and lifestyle factors (i.e., smoking, alcohol consumption, and diets high in fat and low in fiber). Early-stage CRC does not usually present with symptoms. Therefore, screening is necessary to detect cancer at earlier stages. Patients with advanced disease may present with changes in bowel habits, blood in the stool, weakness, fatigue, shortness of breath, signs of intestinal obstruction (i.e., bloating, fullness, cramps, and pain), unexplained weight loss, pain with defecation, and thin stools. In addition to CRC, the differential diagnosis for these symptoms includes hemorrhoids, infection, and inflammatory bowel disease.

The American Cancer Society [13] provides recommendations for guideline CRC treatment by TNM (tumor, nodes, metastasized) stage. Specifically, resection is recommended for stage 0, I, II, and III CRC, and chemotherapy is guideline care for stages III and IV of CRC. Surgery is the most common treatment for CRC with the usual operation being either a segmental resection, partial colectomy, or diverting colostomy in the case of obstruction. Especially for CRCs that have not spread, surgical removal may be curative [14]. The choice of operation depends mainly on the site of the disease (left-sided versus right-sided), the patient's physical condition, nutritional status, and age. The treatment for right-sided lesions is a right hemicolectomy. However, treatment of left-sided lesions is still undecided. There are many therapeutic options such as primary or staged resections, Hartmann's procedure, subtotal colectomy, or colostomy. Other therapies involve nonoperative techniques such as laser therapy, colonic stenting, emergency endoscopy, and comfort measures.

Table 13.1 correlates the stages of CRC with the TNM categories and their associated management.

Trends in CRC incidence and mortality reveal overall declining rates, which have been attributed to reduced exposure to risk factors, early detection through screening, and prevention through polypectomy and improved treatment [15]. However, studies show a majority of US adults are not receiving age- and risk-appropriate screening or have never been screened [11, 16–19]. Among CRC patients, only 39% are actually diagnosed at an early stage, mostly due to these low screening rates [1]. Significant delays in screening translate into worse outcomes in terms of stage of cancer at diagnosis, ability for curative treatment, likelihood of recurrence, and survival, especially among the elderly [20].

Current recommendations for colorectal cancer screening from the US Preventive Services Task Force are presented in Table 13.2.

Table 13.1 Correlation between TNM categories and stage for CRC

Stage	TNM category	Interpretation	Colon cancer management	Rectal cancer management
0	Tis, N0, M0	Early-stage cancer where the cancer is limited to the mucosa of the colon or rectum (Tis). No lymph node involvement (N0) or distant spread (M0)	Surgery	Surgery
I	T1–T2, N0, M0	The cancer has grown through the mucosa into the submucosa (T1) or muscularis propria (T2). No lymph node involvement (N0) or distant spread (M0)	Surgery	Surgery ± radiation
II	T3–T4, N0, M0	T3–T4 stage with no spread to lymph nodes (N0) or distant sites (M0)	Surgery ± chemotherapy	Surgery + chemotherapy + radiation
III	Any T, N1–N2, M0	Any *T* stage with spread to 1–3 (N1) or four or more (N2) regional lymph nodes. No distant spread (M0)	Surgery + chemotherapy ± radiation	Surgery + chemotherapy + radiation
IV	Any T, any N, M1	The cancer can be any *T* stage and any *N* stage and has spread to distant sites such as the liver, lung, peritoneum, or ovary (M1)	Surgery + chemotherapy ± other treatments (RFA, cryosurgery)	Surgery + chemotherapy + radiation

Adapted from the American Cancer Society (2020) [13]
TNM Tumor, nodes, metastasized, *RFA* radiofrequency ablation

Table 13.2 Summary of US Preventive Services Task Force recommendations

Population	Recommendation	Grade
Adults, beginning at age 50 years and continuing until age 75 years	The USPSTF recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years and continuing until age 75 years. The risks and benefits of these screening methods vary	The USPSTF recommends the service. There is high certainty that the net benefit is substantial
Adults age 76–85 years	The USPSTF recommends against routine screening for colorectal cancer in adults 76–85 years of age. There may be considerations that support colorectal cancer screening in an individual patient	The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small
Adults older than age 85 years	The USPSTF recommends against screening for colorectal cancer in adults older than age 85 years	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits
Computed tomographic colonography and fecal DNA testing as screening modalities	The USPSTF concludes that the evidence is insufficient to assess the benefits and harms of computed tomographic colonography and fecal DNA testing as screening modalities for colorectal cancer	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined

Source: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/colorectal-cancer-screening, accessed 11 Jul 2020

The overall relative survival rate for CRC is 65% at 5 years following diagnosis and 58% at 10 years [6]. Forty percent of CRCs are diagnosed at a local stage, for which the 5-year survival rate is 90%. Thirty-six percent of CRCs are diagnosed at regional stage, for which the 5-year survival rate is 70%. Twenty percent of CRCs are diagnosed at a distant stage, for which the 5-year survival rate is 12%.

CRC Diagnosis in the ED

The number of patients presenting to the ED who are subsequently diagnosed with cancer in the ED has increased [21, 22]. In a comparison of patients diagnosed with cancer in the ED versus other settings, patients in the former category were found to be older, have Medicare or Medicaid, have stage IV cancer, and exhibit more symptoms [23]. A population-based study of 11,023 patients in Connecticut reported patients admitted from the ED with a CRC diagnosis were usually older (75+) and African American. An ED admission status was a significant predictor of distant stage in all patients [24]. A study of 151 patients in the United Kingdom examined the pathways to diagnosis of CRC. Despite considerable investment by the UK National Health Service in cancer diagnostic services for primary and specialty practices, 26% of patients had an emergency diagnosis [25].

Diggs et al. [26] focused on predictors and the associated burden of emergency CRC resection (E-CCR), which has been defined as the "clearest evidence on an individual level for a failure of screening" [27]. This cross-sectional study of over 120,000 discharges nationally focused on patients who underwent the procedure emergently, finding older patients dually eligible for Medicare and Medicaid were at higher risk for E-CCR. There was also a threefold increase in hospital mortality, longer lengths of stay, and more than $250 million in additional hospital charges associated with E-CCR. This study was limited in its focus on one type of cancer and a particular procedure associated with CRC.

Early CRC may present to the ED with vague to no symptoms, which further emphasizes the importance of screening. Symptoms that may suggest CRC and the need for additional screening if not already diagnosed with CRC are presented in Table 13.3.

Table 13.3 Emergent symptoms suggestive of colorectal cancer

Bleeding from the rectum
Blood in the stool or in the toilet after having a bowel movement
Dark or black stools
A change in the caliber or shape of the stool (i.e., narrow stools)
Cramping or discomfort in the lower abdomen
An urge to have a bowel movement when the bowel is empty
Constipation or diarrhea that lasts for more than a few days
Decreased appetite
Unintentional weight loss
Weakness and fatigue secondary to anemia

A positive family history of colon cancer should also raise suspicion for CRC on the differential. Findings on physical

exam include grossly positive or guaiac stools. It is important to get basic labs (i.e., CBC and BMP) since blood loss from the cancer leads to anemia, specifically iron deficiency anemia. In the ED, a CT of the abdomen with contrast can help locate and characterize a mass. Timely evaluation of symptoms consistent with CRC is essential, even for adults younger than age 50. If stable, the patient can be discharged with referral to a gastroenterologist for colonoscopy and/or surgeon if a mass is found.

Oncologic Emergencies Associated with CRC

More common is the management of the complications of patients already diagnosed with CRC, which include bowel obstructions, perforations, rectal bleeding, and complications secondary to chemotherapy and radiation. The sections below describe the relationship between CRC and the respective complications and associated history and clinical findings with the appropriate ED management [28].

Bowel Obstruction

As a tumor grows, it may bleed or cause obstruction of the colon. Intestinal obstruction can occur when tumor growth has invaded the lumen of the large intestine. Up to 20% of colon cancer in some series will present as bowel obstruction. This is more likely to occur in the left colon because it is narrower, with the splenic flexure particularly vulnerable [29].

Patients may present with diffuse, colicky abdominal pain, nausea, vomiting, and abdominal distension. They also may have decreased to no bowel movements and flatus. On physical exam, there will likely be diffuse abdominal tenderness and distension with high-pitched or absent bowel sounds. The patient may also be clinically dehydrated and, in advance stages, be hypotensive, tachycardic, and febrile. Labs such as a lactate, CBC, and BMP may be helpful and reveal a metabolic acidosis. Imaging includes an acute series that reveals multiple air-fluid levels, more than 3 cm of dilatation of the small bowel, and/or more than 3 mm thickening of the small bowel (Fig. 13.1).

An abdominal CT can also be very helpful in distinguishing between partial versus complete bowel obstructions as well as to assist in identifying the anatomic location of obstruction (Fig. 13.2). Intussusception primary or meta-

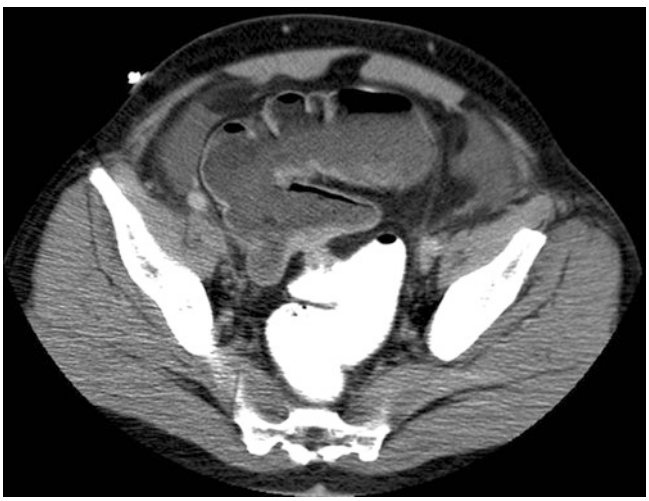

Fig. 13.2 Apple-core obstructing colon cancer following a barium enema demonstrated on an abdominal CT (axial). Note that the contrast material does not pass through the lesion retrograde and the upstream bowel appears to be distended

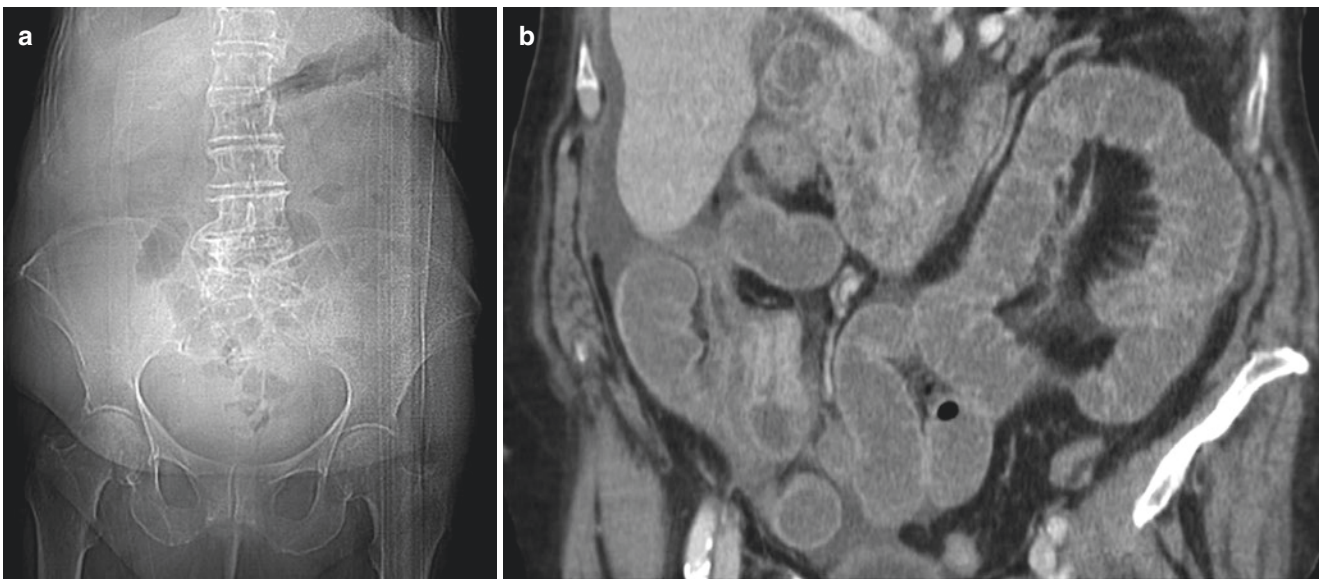

Fig. 13.1 (**a**) Small bowel obstruction on a KUB x-ray due to metastatic lobular breast cancer. (**b**) Coronal CT image revealing a segmental stricture in the right lower quadrant with thickened enhancement of the small bowel wall

static deposits to the bowel can contribute to obstruction (Figs. 13.3 and 13.4).

ED management includes symptomatic treatment with IV fluid boluses, antiemetics, and analgesia. An NG tube may be placed for a significant obstruction, especially if vomiting, and keeping the patient NPO for bowel rest. These patients require admission with gastroenterology and surgery consulting.

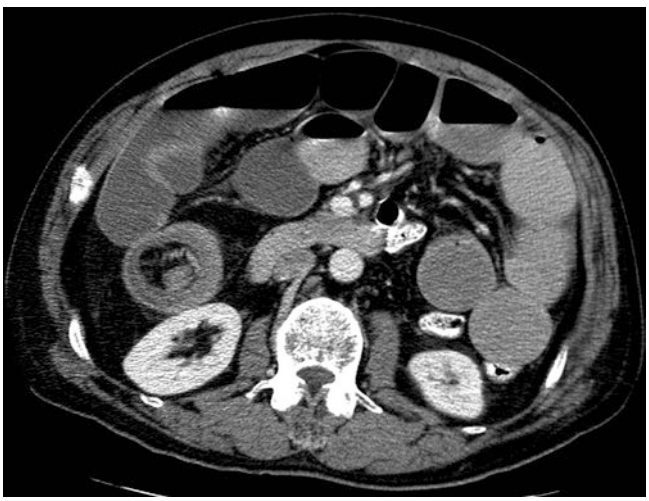

Fig. 13.3 Small bowel obstruction from intussusception secondary to melanoma metastasis, located in the right abdomen in front of the right kidney as demonstrated on an abdominal CT (axial)

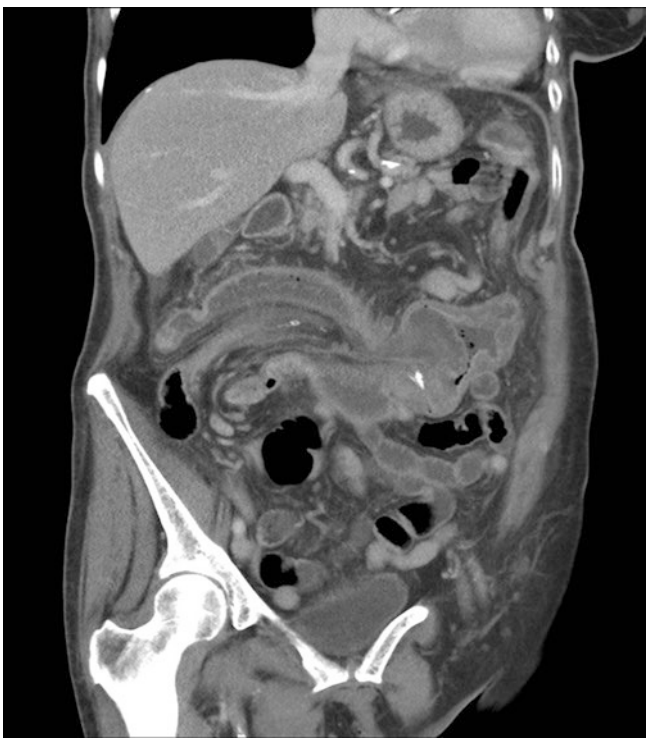

Fig. 13.4 Intussusception from a primary cecal tumor as demonstrated by an abdominal CT (coronal)

Perforation

Patients with CRC may also present with bowel perforations as the CRC invades through the colon wall in more advanced stages. Patients may present with an acute onset of severe abdominal pain possibly associated with near or complete syncope. They are often unable to localize the pain but report worsening pain with any movement (parietal pain). Anorexia is common, but vomiting is often uncommon. On exam, the patient may have acute peritonitis with a rigid abdomen and rebound tenderness. Critical studies include an upright chest x-ray to ensure no air under the diaphragm. Free air can be seen in 70–94% of cases. A CT abdomen/pelvis would be the definitive study if the CXR is inconclusive.

ED management includes IV fluid resuscitation and antibiotics (i.e., 3.375 g of IV Zosyn). Immediate surgical consults are required with patients with perforation.

Rectal Bleeding

Patients with CRC can present with blood in their stools in the setting of recent changes in their bowel habits (i.e., constipation). In general, cancers of the ascending colon tend to be larger and more frequently bleed. Cancers of the descending colon tend to be smaller and more obstructive. Predominant constitutional symptoms include anorexia, fatigue, weight loss, and presyncope. Patients can present from asymptomatic rectal bleeding to ill-appearing with pale conjunctivae, hepatomegaly (secondary to liver metastasis), abdominal or rectal mass, and/or guaiac-positive stools.

Labs include a lactate, CBC, BMP, and coagulation studies. A CBC often reveals microcytic anemia. A BMP can be indicative of an anion gap (lactic) acidosis that is secondary to hypoperfusion. Coagulation studies should be ordered if the patient is anticoagulated or has liver disease.

The ED management depends on the severity of the rectal bleeding. With significant bleeding, two large bore IV lines should be established, and the patient should be volume-resuscitated with normal saline and cross-matched for 2–4 units of blood. If the patient is anticoagulated, FFP may be required to reduce the INR from 1.5 to 2.5. Vitamin K may be needed if bleeding continues despite FFP. General Surgery should be consulted if significant bleeding or obstructive symptoms exist. If stable with an occult lower GI bleed, outpatient oncologic work-up may be appropriate.

Complications Secondary to Chemotherapy and Radiation

Patients in stages 1 and above of CRC may require chemotherapy and radiation which can present to the ED as severe nausea and vomiting. Chemotherapy often causes symptoms

2–3 days after treatment. The emergency medicine approach is dependent on the patient's clinical status. If they appear significantly dehydrated, labs should be drawn to rule out any electrolyte abnormalities. The patient may require IV hydration and antiemetics. The final ED disposition is dependent on the patient's clinical status (i.e., orthostatic, able to tolerate PO, etc.), and the patient's gastroenterologist, hematologist, and/or surgeon should be consulted.

Conclusion

Despite the decreasing incidence of CRC, emergencies secondary to this deadly cancer still exist. It is important for the ED physician to be able to recognize the signs and symptoms that may hint at a new CRC diagnosis as well as how to manage complications in patients with pre-existing CRC. The approach is multidisciplinary with consultation of gastroenterology, hematology/oncologic, and surgery depending on the patient's presentation; however, most important is the emergent recognition and stabilization of these often complex patients.

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Melanoma Screening

14

Wei-Lynn Chong, Thomas M. Pitney, and Michael Sinnott

Case Study

A 23-year-old male is brought in by ambulance after having a syncopal episode on the beach. He is in Australia from the UK over the summer backpacking with friends. Collateral from the ambulance reports that he and his friends have spent the day on the beach and had consumed multiple beers. Temperatures outside have reached 38 degrees Celsius and there was no shade on the beach. He was playing volleyball and had a witnessed collapse where he lost consciousness. His friends placed him on his side and a bystander called the ambulance. There were no witnessed shaking movements or incontinence. After a couple of minutes, he regained consciousness and has Glasgow Coma Scale score of 15 since that time.

He reports a few days of heavy alcohol intake prior to today and has spent the weekend on the beach in the sun. He has no other medical conditions and denies any regular medications or recreational drug use. His examination reveals blistering sunburn to his face, trunk and upper limbs. His examination reveals normal vital signs except for a postural tachycardia, dry mucus membranes and an incidental finding of multiple melanocytic naevi with a large, irregular lesion on his lower back. Investigations of a bedside electrocardiogram, full blood count and biochemistry panel reveal a mild prerenal acute kidney injury consistent with dehydration. The impression is that the patient has had a syncopal event secondary to dehydration from sunburn, heat exhaustion and excess alcohol intake. The plan for his management in the emergency department includes IV fluid therapy, application of soothing gels to his sunburn, teledermatology referral for review of the lesion on his lower back and education on sun protection and alcohol consumption. On discharge his vitals have normalised and he is feeling much better. He has an appointment with dermatology in 3 days for consideration of excision of the lesion on his back. He was given written and verbal advice about sun protection, including wearing sunscreen, a hat, sunglasses and clothing to protect himself from the sun when outside, as well as to avoid being in direct sunlight between 10 am and 2 pm.

Introduction

In both the USA and Australia, skin cancer is the most commonly diagnosed malignancy. Importantly it is also the most easily preventable and most successfully treated when diagnosed early [1]. Although less common than basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), melanoma is more important to diagnose early due to its high metastatic potential and mortality risk. A melanoma is a malignant tumour arising from melanocytes. It is easily treatable if detected at an early stage. In situ lesions (confined to the epidermis) have a very low risk of metastatic spread. The main risk factor for metastasis and mortality is the depth of dermal invasion [2].

Given the importance of early detection, melanoma has been the focus of many primary prevention programmes in Australia, notably the "Slip, Slop, Slap" campaign of the 1980s, which encouraged the public to Slip on a shirt, Slop on sunscreen and Slap on a hat to limit excessive sun exposure [3]. There is evidence that this has been effective, with a noted age-specific decrease in incidence of melanoma in the 0–39 age group from a peak of 13 to 9.4 per 100,000. The same data reveal a decreased incidence of invasive melanomas in the under 55 group and a slower increase than prior in

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the above 55 group [4]. Unfortunately, the proportion of thick melanomas at initial diagnosis has not changed over time. This is thought to reflect their highest incidence in older people, particularly men, to whom little specific advertising or primary prevention campaigns have been directed. This increasing incidence with age will become more relevant over time as populations age in the western world.

The burden of skin cancer in Australia is largely managed by public outpatient "general practitioner" physicians, with a smaller number being managed in public or private hospital outpatient clinics and very little being specifically managed by the urgent care or emergency physician. The importance of the emergency department (ED) in melanoma prevention and screening is in its valuable contact with people who may most benefit, such as those from lower socioeconomic groups. They may have poorer health literacy and have been shown to have poorer melanoma prognosis [5]. An unrelated ED visit for an emergency issue may be their sole point of contact with the medical profession for extended periods of time and an important opportunity to provide both primary prevention advice with sun protection, self-identification of suspicious lesion education and a secondary screening chance while addressing their primary presenting issue.

Opportunistic at-risk groups may include ED presentations for sunburn, or patients with melanoma risk factors such as a personal or family history of melanoma and other solar-related skin malignancies, solar damage, multiple naevi or immunosuppression. Other at-risk groups include young people without a primary healthcare physician. Identification of these groups with referral to specialist services when appropriate has demonstrated both improved outcomes for the patients and cost-effectiveness compared to standard community care. In a 2017 cost-effectiveness study, over a 10-year period, specialised surveillance services were estimated to result in a savings of $6828 (in 2013 Australian dollars) and a gain of 0.31 quality-adjusted life-years per patient when compared to standard care [6].

Epidemiology

Melanoma has an incidence rate of 49 per 100,000 in the Australian population and a mortality rate of 6.2 per 100,000 (standardised for age). Melanoma accounts for 10% of all cancers diagnosed in Australia and for 3.8% of cancer deaths [1].

Risk factors for melanoma are both environmental and genetic. Environmental ultraviolet (UV) radiation exposure from the sun with repeated significant sunburns appears to carry the greatest risk [7]. Sunbed (tanning bed) use is considered an independent risk factor, particularly if first exposure occurs before the age of 35 [8].

Genetic factors may increase risk of melanoma. Phenotypic features associated with this risk are skin types having poor ability to tan and higher risk of sunburn, including those with fair complexion, blond or red hair and pale eyes. Large numbers of melanocytic naevi are also associated with increased risk of melanoma. Other clinical features indicating higher risk include skin changes associated with solar damage, such as freckling, solar elastosis, solar lentigines and keratoses [8–11]. Conversely, darker-skinned groups have a lower incidence of melanoma primarily as a result of photoprotection provided by increased epidermal melanin, which filters twice as much UV radiation as does that in the epidermis of fair-skinned groups [9]. As such melanoma demonstrates greater variation in incidence rates across different ethnic groups than that of most cancers [10].

Although skin malignancies occur less frequently in those with dark skin types, they suffer from higher rates of mortality and morbidity. This is likely due to delayed diagnosis [9]. Though UV radiation exposure is not as significant compared to those with high-risk phenotypic features, sun protection is still advised to protect from basal cell carcinoma development.

A personal or family history of melanoma in parents or siblings is associated with increased risk. Having a parent with multiple melanomas is a particularly strong risk factor [12].

Pathophysiology

UV radiation (wavelength 100–400 nm) can be classified as UVC (100–280 nm), UVB (280–315 nm) and UVA (315–400 nm). All UVC and 90% of UVB are absorbed in the atmosphere. UV radiation has been implicated in the development of cutaneous melanoma. The precise mechanism of this pathogenesis is poorly understood; however, both UVB and UVA are implicated. UVB-induced mutations of the phosphatase and tensin homologue (PTEN) tumour suppressor gene, by direct DNA base pair damage, have been demonstrated in melanoma samples from patients with xeroderma pigmentosum [11]. UVA, which penetrates deeper into the dermis of the skin than UVB, can itself induce DNA damage through production of radical oxygen species and exerts an immunosuppressant effect which may also contribute to the development of melanoma [12].

Clinical Manifestations

Melanoma can present in a multitude of ways. Clinical features vary with melanoma subtype, tumour width and thickness, the anatomical site, the presence of regression or inflammation and even patient skin type (Table 14.1 [13, 14];

Table 14.1 Melanoma subtypes

Type	Incidence	Clinical features
Superficial spreading (Figs. 14.1 and 14.2)	Most common subtype in fair skin, rare before 4th decade	50% develop in a pre-existing naevus, and there may be clinically contrast between these two components [13]. Generally macular in early stages but can develop nodular components as it progresses
Nodular (Fig. 14.3)	Incidence peaks in 5th to 6th decade of life	Most common on the trunk region. Has rapid vertical growth pattern
Lentigo maligna (Fig. 14.4).	Elderly population	Often progress very slowly through an in situ phase from a pre-existing solar lentigo, usually on a sun-damaged skin background. Increase in size, depth of colour and irregularity of pigment are clues that suggest malignant change
Acral lentiginous (Fig. 14.5)	10% of melanoma on white skin but over 50% on darker skin types [14]	Appear as an irregular lentiginous pigmented area on the sole or palm of the hand
Subungual (Fig. 14.6)	Rare. Proportionally more frequent in darker skin types in 40–70 age group	Arise from the nail matrix and present as melanonychia (brown pigmentation of the nail). Extension of pigmentation onto the proximal nail fold (Hutchinson sign), heterogeneity of pigment colour, expansion of the width of pigment distribution and proximal growth are concerning features that separate from benign longitudinal melanonychia

Figs. 14.1, 14.2, 14.3, 14.4, 14.5 and 14.6). Lesions that are symptomatic, stand out from other naevi (the "ugly duckling" sign) or have a history of change should be examined closely. Dermoscopy is an essential tool to identify key features of malignant change but requires specific training in its use to be of benefit [15].

Commonly taught tools for both physicians and self-assessment of skin lesions (such as ABCDE mnemonic) are

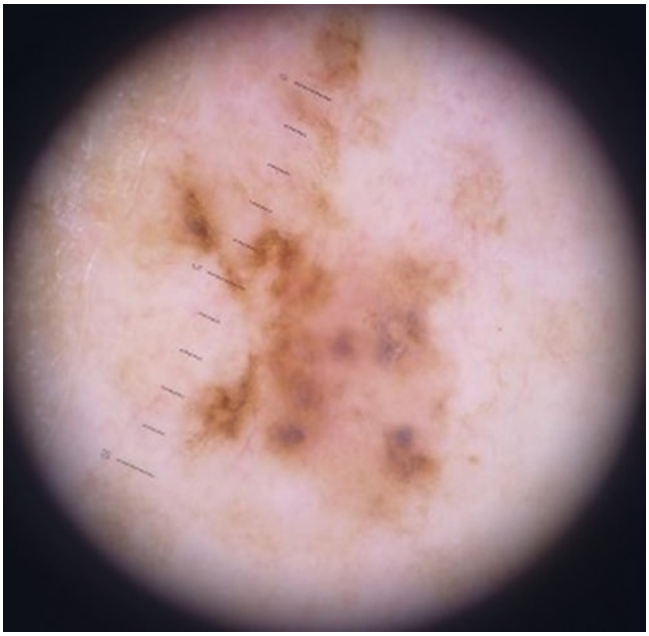

Fig. 14.1 Dermoscopy image of Fig. 14.2a (superficial spreading melanoma)

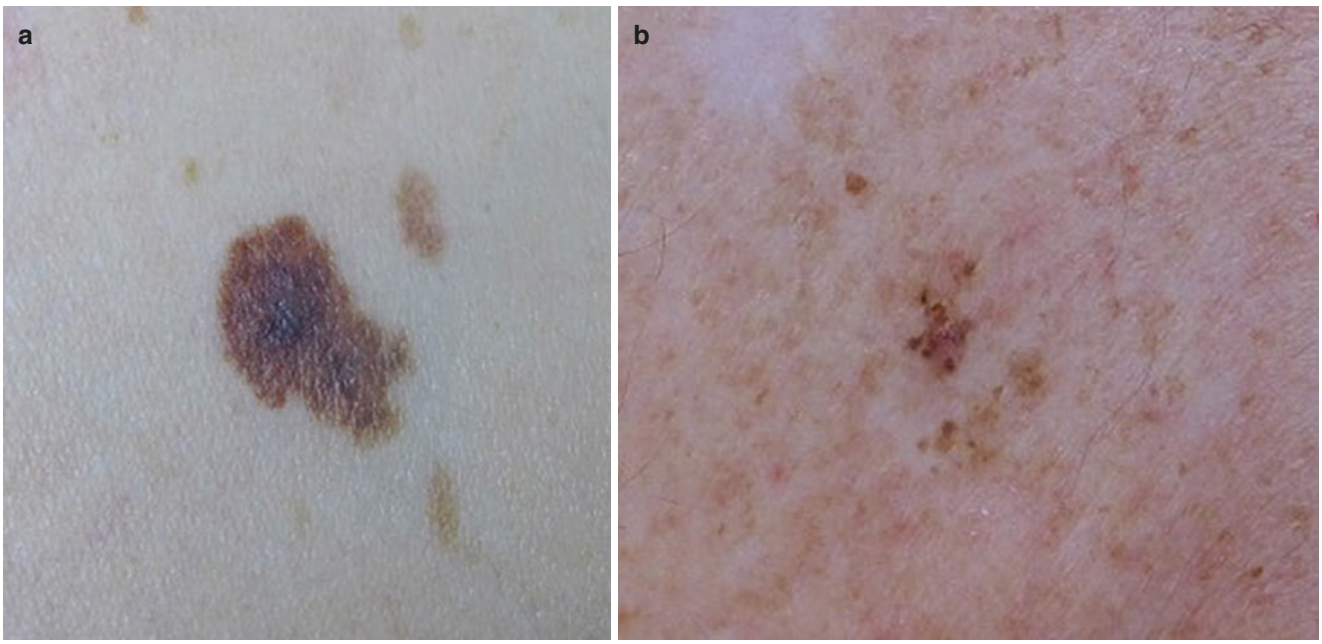

Fig. 14.2 (**a**, **b**) Superficial spreading melanoma

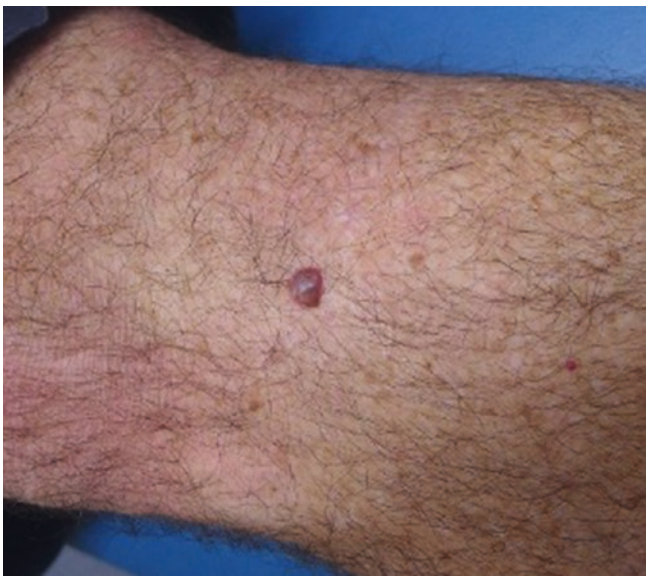

Fig. 14.3 Amelanotic nodular melanoma

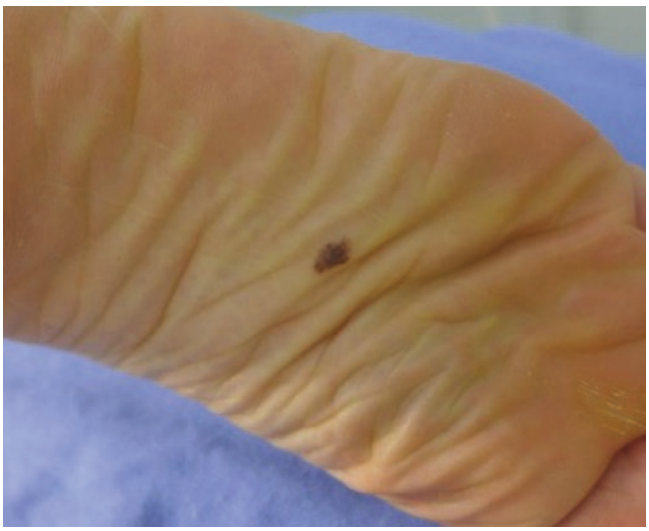

Fig. 14.5 Acral lentiginous

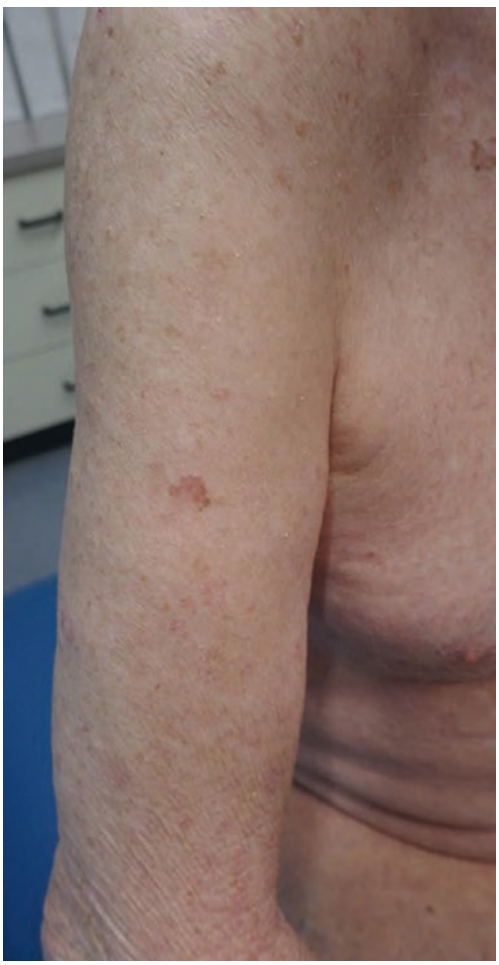

Fig. 14.4 Lentigo maligna

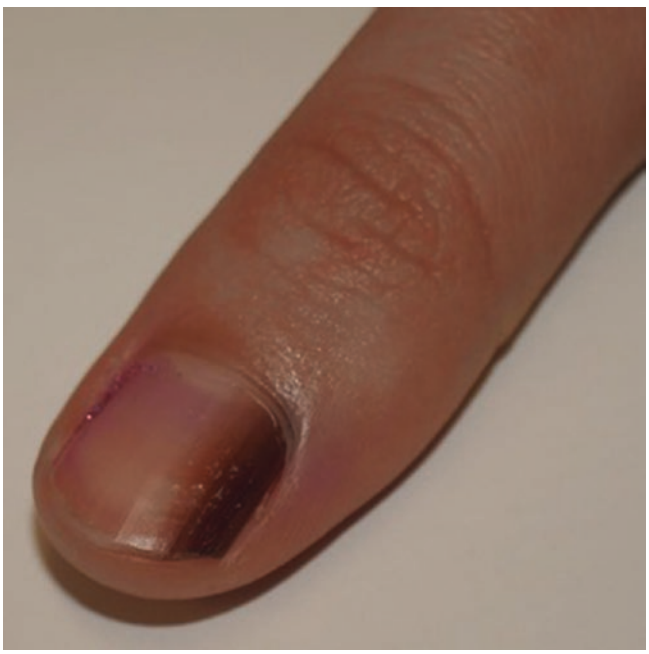

Fig. 14.6 Subungual melanoma

simple enough that patient education should be attempted in patients considered at risk [16]. This mnemonic reminds the patient to look for Asymmetry, Border Irregularity, Colour that is not uniform, Diameter (larger than a pea) and Evolving size, shape or colour.

Any of the above variants can also rarely be amelanotic, appearing as "skin coloured" or red, pink or purple discoloured areas with or without nodular components.

Teledermatology

Technological advancements in dermatology over the last two decades include the introduction of teledermatology into healthcare organisations worldwide to expand the availability of specialty services. Teledermatology is an innovative model of care and an alternative to traditional face-to-face specialist consultation. Primary referral physicians have greater and faster access to specialist dermatology opinion, and dermatologists are able to increase their work-flow efficiency through this method. There are two applications of teledermatology: (1) live interactive and (2) store and forward technologies; or a combination of both can be utilised [17]. Live interactive teledermatology involves live conferencing between the primary healthcare worker with the patient and specialist dermatologist. Store and forward technologies utilise still images and written clinical referral or over the phone referral to specialist dermatologists. Dermatology is a visual specialty and as such is highly suited to the use of digital images for diagnostic and disease management purposes [13].

The benefits of teledermatology are immense. Same-day access to dermatology opinion allows primary referral physicians, especially those in rural and regional areas, increased access to specialist services to improve their diagnosis, initiate treatment and reduce morbidity and mortality related to misdiagnoses or treatment delay [17, 18]. Successful programmes initiated in Queensland, Australia, revealed the highest number of external referrals came from a rural hospital, located 1200 km from the nearest dermatology clinic and that junior physicians represented the majority of referring clinicians [19]. Decreasing the number of second referrals to a dermatologist produces a reduction in cost burden with savings in patient travel times and wait times [18]. Teledermatology may also help address projected dermatology workforce shortages.

However, the limitations of teledermatology should be recognised. Live interactive teledermatology requires more initial financial investment compared to store and forward technology and is at the mercy of provider networks that may be unpredictable in rural areas and provide poor image quality [17]. Technological advances, increased consumer use of smart phones, increasing use of email, faster internet speeds and maturation of electronic health records may mitigate these downsides [20]. Medicolegal risks involving patient privacy and confidentiality are inherent in use of personal phones and emails as platforms to relay potentially sensitive patient information. Practitioners attempting to limit their legal liability in the event of a breach of privacy should demonstrate that reasonable measures were taken to protect patient information. This includes obtaining patient consent before using teledermatology, blocking auto-uploads of clinical images from clinician's devices, encrypting or password-protecting images before transmission, deleting any patient information from personal email accounts or devices after use and securely storing any video recording of consultations [13]. Use of hospital or hospital-approved camera devices, work emails and institution-approved messaging platforms is preferred over personal equipment.

Investigation and Diagnosis

Definitive diagnosis can be difficult to make clinically in some cases. Excisional biopsies of any suspicious lesions are necessary for definitive diagnosis. Often, biopsy is not logistically possible in a busy ED, and responsibility falls to the local general practitioner, dermatologist or surgeon. Clear communication between the ED and the local physician (ensuring precise documentation of the lesion so both physician and patient are aware of its location) and educating the patient on the importance of following up this appointment to have the lesion biopsied is essential. Disadvantaged groups may benefit from having these appointments organised for them to improve compliance. If admitted, seeking consultation from inpatient dermatology or surgical teams can expedite the investigation and management of suspected lesions.

If melanoma has been considered as a diagnosis, the patient should be examined for evidence of regional or systemic dissemination. This involves palpation of draining lymph nodes and exclusion of hepatosplenomegaly in the first instance. Urgent biopsy and appropriate investigation and treatment should occur.

Metastasis of melanoma occurs through regional lymph node disease in 63%, direct haematogenous spread in 24% and satellite deposits in 13% as their first site of metastasis [21].

Treatment

The recommended initial management of any suspected melanoma is complete excisional biopsy with 2 mm margin into the subcutis. Lesions that are small and appear minimally invasive may be amenable to techniques such as deep shave excision (saucerisation) or punch excisional biopsy; however, these may risk deep or lateral margin involvement and require skill and practice to perform reliably. Partial biopsy techniques should be avoided if possible.

The most important prognostic factor remains Breslow depth – the degree to which the lesion has penetrated into the skin. This is shown by diagram in Fig. 14.7.

The depth of subsequent wide local excision for melanoma is dependent on maximum Breslow thickness.

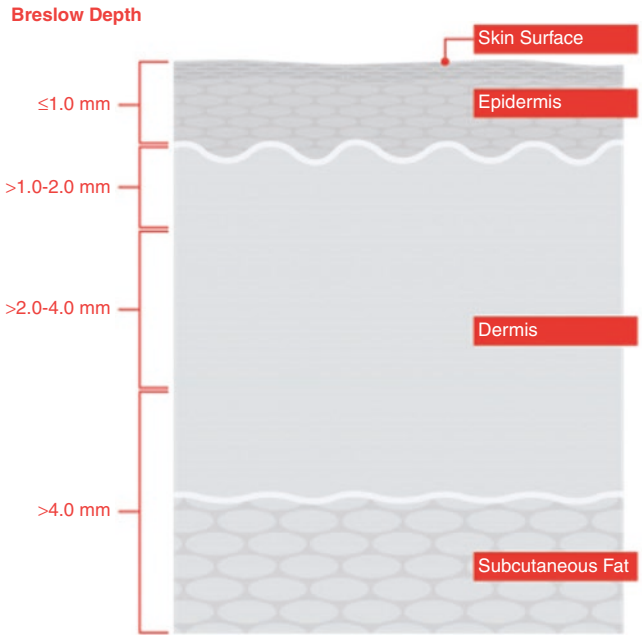

Fig. 14.7 Breslow thickness (Courtesy and with permission of the Melanoma Research Alliance, Washington, DC)

Table 14.2 Breslow thickness and 10-year survival [23]

Breslow thickness (mm)	Recommended clear surgical margin	10-year survival
In situ	5–10 mm	–
<1	1 cm	92%
1.01–2	1–2 cm	80%
2.01–4	1–2 cm (2 cm suggested when possible to achieve, particularly if concerning high-risk features)	63%
>4	2 cm	50%

Recommended clear margins for increasing depth are detailed in Table 14.2 [22, 23].

Metastatic risk and subsequent mortality are strongly linked to the Breslow depth. Those with in situ or very superficial melanoma (<0.78 mm) will have high (95–100%) 5-year survival rates. Thicker lesions or metastatic lesions predict poorer survival (see Table 14.2). The most recent classification guidelines also take into account other factors such as localised tumour characteristics (ulceration, mitotic rate), lymph node involvement, metastasis location and biochemical blood markers such as lactate dehydrogenase.

There is no uniform indication for performing a sentinel lymph node biopsy in patients diagnosed with cutaneous melanoma. Current Australian recommendations suggest that melanomas with >1 mm Breslow depth or >0.8 mm with high-risk features will benefit. High-risk features include presence of mitoses, ulceration or lymphovascular invasion or age <40 years old [24]. Sentinel node biopsy provides useful prognostic information, but is not recommended for all cases due to complications associated with the general anaesthesia and documented risks of seroma, infection, false negatives (higher in certain locations such as head and neck) and lymphedema.

The role of PET or CT scanning is dependent on stage of disease. Patients with asymptomatic Stages 1–2 (localised disease with no sentinel lymph node positivity if applicable for testing) are not recommended for further investigation, only routine follow-up with full skin checks every 6–12 months [25]. Patients with sentinel lymph node positivity or thick tumours with high-risk features should be considered for imaging on a case-by-case basis, or if specific symptoms suggestive of metastasis exist (in consultation with medical oncologic).

The Future of Diagnosis

Research involving artificial intelligence (AI) to develop algorithms that diagnose early melanoma as well (or better) than physicians has sparked much debate over the benefits and harm of incorporating this technology into clinical practice [26]. The potential benefits of AI are numerous; however, more research is needed, and governance needs to be established, prior to implementation of AI into clinical practice. Given the ethical and medicolegal issues involved, it will be important to maintain close clinical oversight when AI is employed. Its best current use may be as a supplement to clinician diagnosis. AI cannot substitute for the physician's ability to integrate historical data with physical examination findings in generating a differential diagnosis and management plan. Clinical assessment is a multifactorial, unpredictable and complicated process. However, with technological advancement this may change. The challenge of preventing diagnostic skill decay in AI-assisted dermatology must be recognised as well as the potential risk for layperson misuse of downloadable smartphone applications [27].

The diagnostic accuracy of AI is limited by the accuracy of histopathological diagnoses that feed into its algorithms and neural networks. While pathologist-interpreted diagnoses are considered the current gold standard, there is clear acknowledgement that interobserver variability exists, particularly with "borderline" lesions (Lallas, Elmore) [26, 28]. Further research is required before the integration of AI into mainstream clinical practice.

Primary Prevention

Numerous primary prevention strategies to reduce UV radiation exposure to the general population exist worldwide. From community awareness campaigns to workplace education, as well as legislation against tanning bed use, these policies have resulted in a higher early detection rates for melanoma.

Fig. 14.8 Can you spot a skin cancer? Community awareness campaign poster (Courtesy and with permission of SunSmart, Cancer Council Western Australia)

Sunscreen contains chemicals that absorb and reflect UV radiation. The sun protection factor (SPF) measures a sunscreen's effectiveness at protecting against sunburn [29]. Effective sun protection health campaigns target the population on an individual, workplace and community level. In Australia, one of the most successful health campaigns was launched by Cancer Council Australia, a non-government organisation, in 1981. Their "Slip, Slop, Slap" campaign has evolved into a multicomponent programme targeting both primary and secondary screening practices. It advocates regular skin checks at an individual level and provides advice and resources (e.g. factsheets and online courses) for schools, early childhood facilities, workplaces, sport groups, community events and health professionals, as well as local government. Figure 14.8 is of a poster targeting regular skin checks as part of the "Slip, Slop, Slap, Seek, Slide" sun protection campaign. In 2019, nearly 40 years after the launch of this health campaign, Australia achieved its highest rate of early melanoma detection, with over 90% of cases diagnosed as Stage 1 or 3 [1]. Melanoma has near 100% 5-year survival when diagnosed at Stage 1.

Sunbed (tanning bed) use is associated with a significant increase in melanoma risk. This risk increases with the number of tanning sessions and with initial exposure at a young age (<35 years) [30]. In 2003, the World Health Organisation published *Artificial Tanning Sunbeds: Risk and Guidance*, outlining the role of UV radiation from the sun and artificial sources in the development of skin cancer (https://www.who.int/uv/publications/sunbedpubl/en/). Subsequently, legislative changes in Brazil and Australia led to a ban on the commercial use of tanning beds.

Other sun protection regimes include municipal planning policies outlining the importance of access to services and facilities providing protection from solar UV radiation, such as shade provision in public places like bus stops, parks, playgrounds and sporting and recreational facilities. Signage at community events encouraging sun protection is also encouraged.

Health professionals prescribing medications known to cause photosensitivity such as certain antibiotics, antiarrhythmics and antihistamines should counsel patients to avoid direct sunlight while taking these medications as well as about the importance of SPF in sunblock choice. Similarly, care for patients presenting to the ED with UV radiation (i.e. sunburn) should include opportunistic counselling regarding sun protection in the future.

Secondary Screening

Secondary prevention or early detection by means of full skin examinations is recommended, especially for individuals at high risk of melanoma. A structured surveillance protocol with 6 to 12 monthly full skin examinations, supported by total body photography and dermoscopy, is proven to be beneficial both clinically and economically [6]. There is no general consensus on timing of first skin check and intervals between skin checks. Educating high-risk individuals to recognise and document suspicious lesions is recommended [31].

Full skin examinations in the ED are not routinely completed due to time constraints and lack of follow-up by the same physician. Identification of a suspicious lesion opportunistically in the ED warrants follow-up through referral to dermatology or to a general practitioner for consideration of biopsy. However, presentation to an ED by at-risk populations with poor health literacy may be the only opportunity to diagnose, educate and encourage urgent follow-up of high-risk individuals.

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Part III

Evaluation and Treatment

Acute Airway Obstruction

15

Christopher H. Chang and Lakshmi Mudambi

Case Study

*A 65-year-old male presented with 2 months of large-volume hemoptysis. Prior medical history included Child-Pugh Class B cirrhosis with thrombocytopenia and hypothyroidism. He was an active smoker with a 110 pack-year smoking history. Computed tomography showed a right upper lobe mass extending into the right mainstem and post-obstructive pneumonitis of the right upper lobe (*Fig. 15.1*, arrow). A positron emission tomography (PET) scan showed no distant or nodal metastasis (*Fig. 15.2*). Rigid bronchoscopy was performed to debulk and cauterize the tumor (before and after therapeutic bronchoscopy pictures), which controlled the hemoptysis. The patient was not a candidate for surgical resection due to his poor functional capacity and advanced hepatic disease, so he underwent definitive radiotherapy for a cT2aN0M0 squamous cell carcinoma of the right upper lobe.*

Introduction

Malignant central airway obstruction (MCAO) is defined as a mechanical obstruction of the trachea or either mainstem bronchi impairing airflow to the lungs due to a malignant neoplasm.

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Epidemiology

The most common cause of MCAO is a primary lung cancer with approximately 20–30% of patients with lung cancer developing symptoms related to central airway obstruction. MCAO can also occur due to metastasis from a solid organ malignancy, most commonly breast cancer, colorectal can-

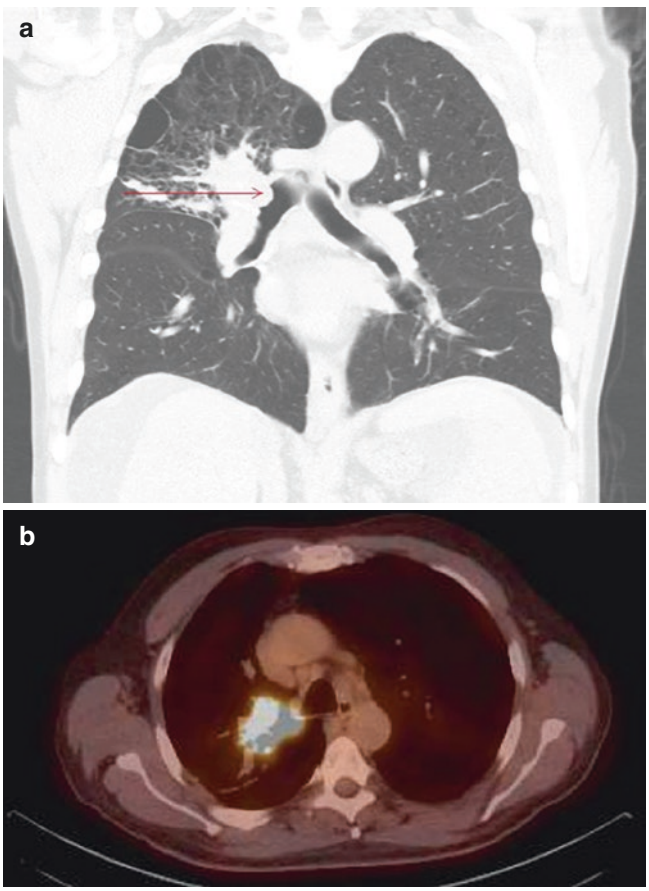

Fig. 15.1 (**a**) Computed tomography revealed a right upper lobe mass extending into the right mainstem (*arrow*) and post-obstructive pneumonitis of the right upper lobe. (**b**) A positron emission tomography scan showed no distant or nodal metastasis

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cer, and renal cancer [1]. It can result from external compression or direct invasion from tumors of adjacent structures such as the esophagus, thyroid, and mediastinum [2]. Other causes of MCAO include carcinoid tumors, which account for the majority of primary tumors distal to the main carina, and primary malignancies of the trachea [3], such as squamous cell carcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma.

Classification

Bronchoscopy is used to characterize the appearance of the tumor and may be classified as an endoluminal (intrinsic), extraluminal (extrinsic), or mixed tumor. Endoluminal obstruction is caused by an exophytic lesion growing into the lumen of the airway. Extraluminal obstruction occurs when a tumor that is adjacent to an airway compresses the lumen. When both endoluminal and extraluminal obstruction occur from a tumor, it is classified as a mixed obstruction. The distinction between these types of obstructions is critical to developing a management strategy.

Presentation

The presentation of MCAO is variable, ranging from asymptomatic to catastrophic. Patients with MCAO present with a persistent dry or productive cough, dyspnea with exertion or at rest, wheezing, hemoptysis, or post-obstructive pneumonia. Stridor at rest suggests a tracheal diameter of less than 5 mm [4]. The diagnosis of MCAO can be elusive as many of these symptoms overlap with other diseases such as asthma, chronic obstructive airways disease, and pneumonia.

The development of dyspnea in an individual with MCAO is the result of an intricate interaction of multiple factors (Fig. 15.3). The sensation of dyspnea from a central airway obstruction is postulated to occur from the increased effort required to maintain airflow through a narrowed lumen [5]. Significant airway obstruction is defined as an endoluminal diameter of <50% of normal, but individuals who are otherwise healthy enough to generate sufficient negative intrathoracic pressure to overcome the increased airflow resistance are often able to tolerate much greater degrees of obstruction without symptoms. Factors such as the increased metabolic demand, cachexia from cancer, and the presence and severity of cardiac, pulmonary, and renal comorbidities also contribute to the sensation of dyspnea. Interestingly, some patients with significant MCAO and severe comorbidities may report being minimally symptomatic but only by limiting their activities.

Some symptoms may be dramatic and warrant urgent or emergent intervention. Hypoxemia that is refractory to supplementary oxygen or noninvasive ventilation can occur suddenly due to acute lobar atelectasis or after a period of slowly progressing dyspnea. Massive hemoptysis or hemoptysis associated with respiratory compromise creates urgent clinical situations that require immediate action. Post-obstructive pneumonias may not be responsive to antibiotics without relief of obstruction, can progress to sepsis, and preclude treatment with systemic chemotherapy.

Acute airway obstruction may also arise from complications related to prior treatment of MCAO. For example, radiotherapy is used extensively in the treatment of intrathoracic malignancies, and several reports of high-grade toxicities of the airways such as massive hemoptysis, airway necrosis, bronchial stenosis, and fistulas leading to central airway obstruction have been documented [6–9]. Airway stents can also lead to respiratory distress due to complications such as stent migration, stent fracture, and obstruction of the stent

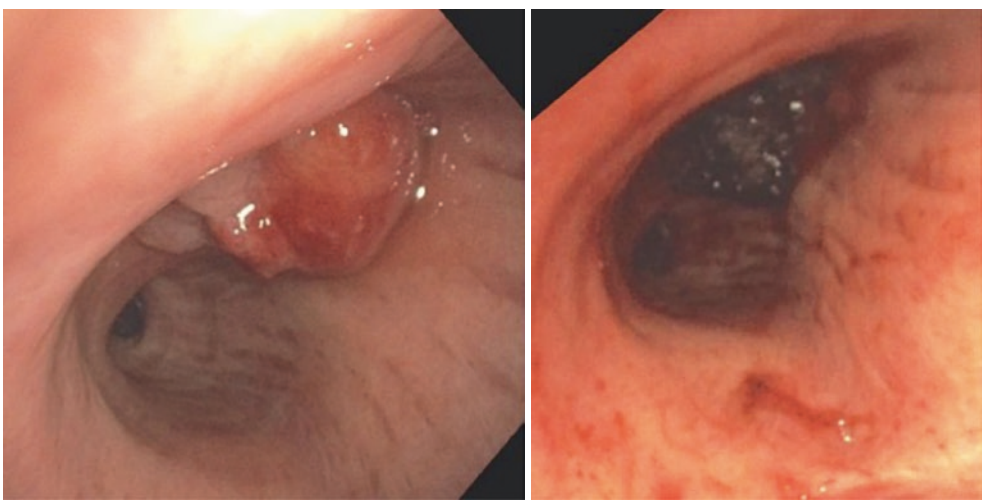

Fig. 15.2 Before (*left*) and after (*right*) images from therapeutic bronchoscopy in which the mass tumor was debulked and cauterized

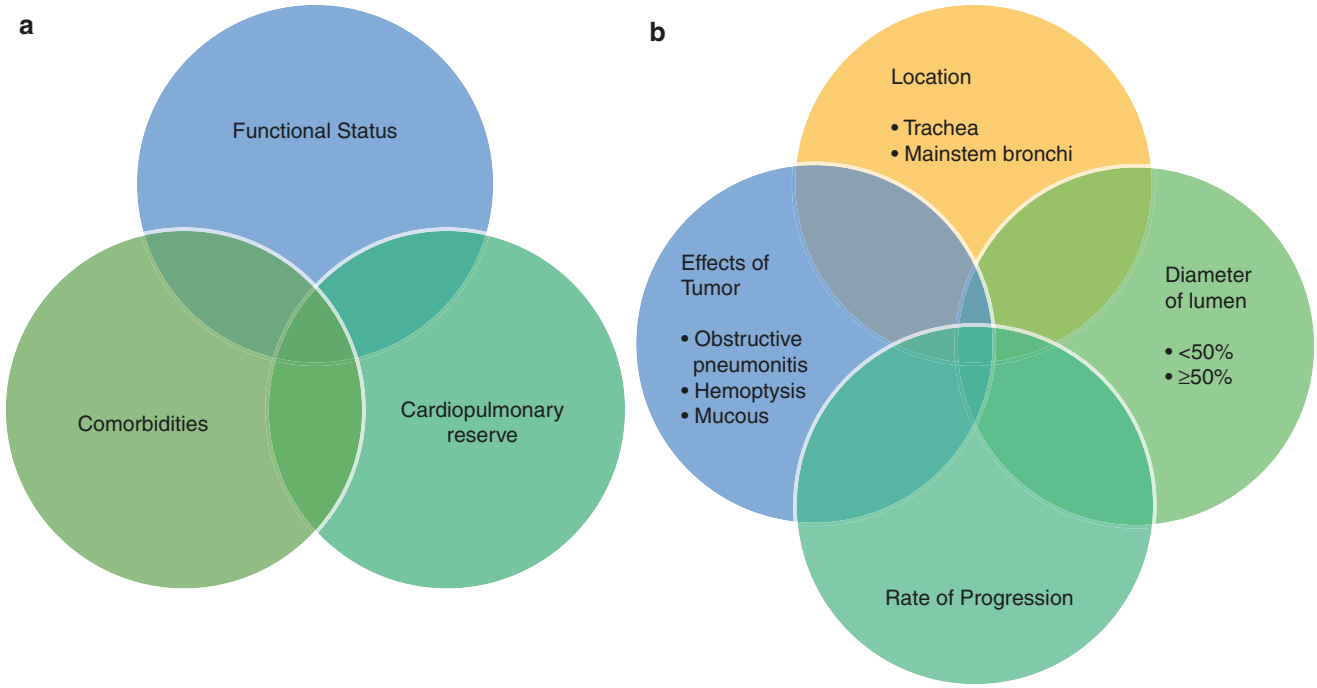

Fig.15.3 (**a**) Patient characteristics involved in the development of symptoms in malignant central airway obstruction (MCAO) (**b**) Tumor characteristics involved in the development of symptoms in MCAO

with mucous plugs or granulation tissue [10]. Although these situations cannot be purely designated as MCAO, it is reasonable to include them in this context since they present in the same patient population and can be life-threatening.

Evaluation

In addition to obtaining a complete history and performing a thorough clinical examination, radiographic imaging and bronchoscopy are useful tools to evaluate MCAO. Although plain radiographs are not very sensitive to detect MCAO, they may be the only imaging modality tolerated by a patient in respiratory distress. Plain radiographs can help determine laterality of the malignancy and show lobar or lung collapse, compression of the large airways, and lung masses. A computed tomography of the chest provides valuable information regarding the extent, location, morphology, and relationship of the tumor with surrounding structures, which is necessary for procedural planning [11, 12]. It is also useful to review prior imaging as the information obtained about the progression and rate of growth of a tumor can aid decision-making for both management and prognostication. Although flexible bronchoscopy is the gold standard diagnostic tool to assess MCAO, extreme caution must be employed as even gentle manipulation of a critical malignant airway obstruction can cause bleeding and edema resulting in an airway emergency, especially if immediate access to equipment and skilled personnel are unavailable to manage these compilations. In patients with large anterior mediastinal masses, the use of sedatives and paralytic agents for intubation, bronchosocpy or other procedures can cause complete airway collapse and respiratory arrest due to extrinsic compression of the airways [13]. In such situations, it is important to establish an airway that traverses the collapsed segment and can be secured either by an awake bronchoscopic intubation, rapid sequence intubation or rigid intubation.

Management Overview

The approach to the management of MCAO begins with an assessment of symptoms and the extent of disease. Interventional pulmonology, thoracic surgery, otorhinolaryngology, and interventional radiology play collaborative and complementary roles in the management of MCAO depending upon location and presenting symptoms. In a true emergency, resuscitation and stabilization are the primary aims. In impending or complete obstruction without access to specialized care, awake bronchoscopic intubation with a small-diameter, wire-reinforced endotracheal tube is an effective method to secure an airway in a critical malignant obstruction proximal to the main carina. Bronchoscopic guidance helps prevent excessive trauma to the tumor, thereby reducing the risk of hemorrhage while advancing the endotracheal tube past the obstruction. Rarely, in patients with dyspnea without significant hypoxemia, heliox can be used to reduce

resistance to airflow across the malignant obstruction as a bridge to therapeutic bronchoscopy.

It is paramount to objectively define goals of an intervention in MCAO. Aside from addressing urgent or emergent clinical situations, therapeutic bronchoscopy has been shown to improve dyspnea, spirometry, walk distances, survival, and, most importantly, quality of life [14–17]. Additionally, patients with greater dyspnea and poorer functional status derive the most benefit from therapeutic bronchoscopy [18]. A large, prospective review from the multicenter AQuIRE registry showed that complication rates of therapeutic bronchoscopy are low, averaging 3.9%; however, there is significant variability between institutions (0.9–11.7%) [19]. Although overall survival in MCAO is dependent upon the underlying malignancy, therapeutic bronchoscopy can bring significant relief and comfort as a palliative intervention [20].

In operable patients with MCAO and minimal symptoms, it may be reasonable to proceed to surgery as the first step with the goal of curative treatment (Fig. 15.4). Sometimes, symptoms like large-volume hemoptysis necessitate therapeutic bronchoscopy to prevent complications such as respiratory failure before considering treatment for the underlying malignancy (Fig. 15.5). The lobar airways distal to the central obstruction should be patent and spared from tumor infiltration when contemplating therapeutic interventions to alleviate dyspnea and recanalize the lumen. This can usually be identified on cross-sectional imaging and bronchoscopy, using thin scopes to explore past the central lesion (Fig. 15.6). Patency of distal airways, either on CT or bronchoscopy, has been identified as predictors of a successful therapeutic bronchoscopy to relieve MCAO [18, 21]. Control of hemoptysis

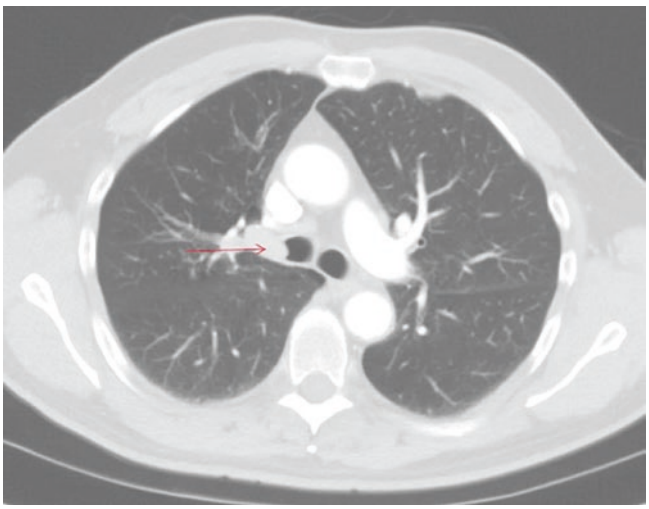

Fig. 15.5 61-year-old male with large-volume hemoptysis and respiratory distress. Computed tomography of the chest showed a well-circumscribed 2.5 cm nodule in the right upper lobe bronchus extending into the right mainstem (*arrow*). A rigid bronchoscopy was performed to debulk and cauterize the tumor. Two months later, he underwent a video-assisted thoracoscopic lobectomy for a pT1bN0M0 squamous cell carcinoma of the right upper lobe

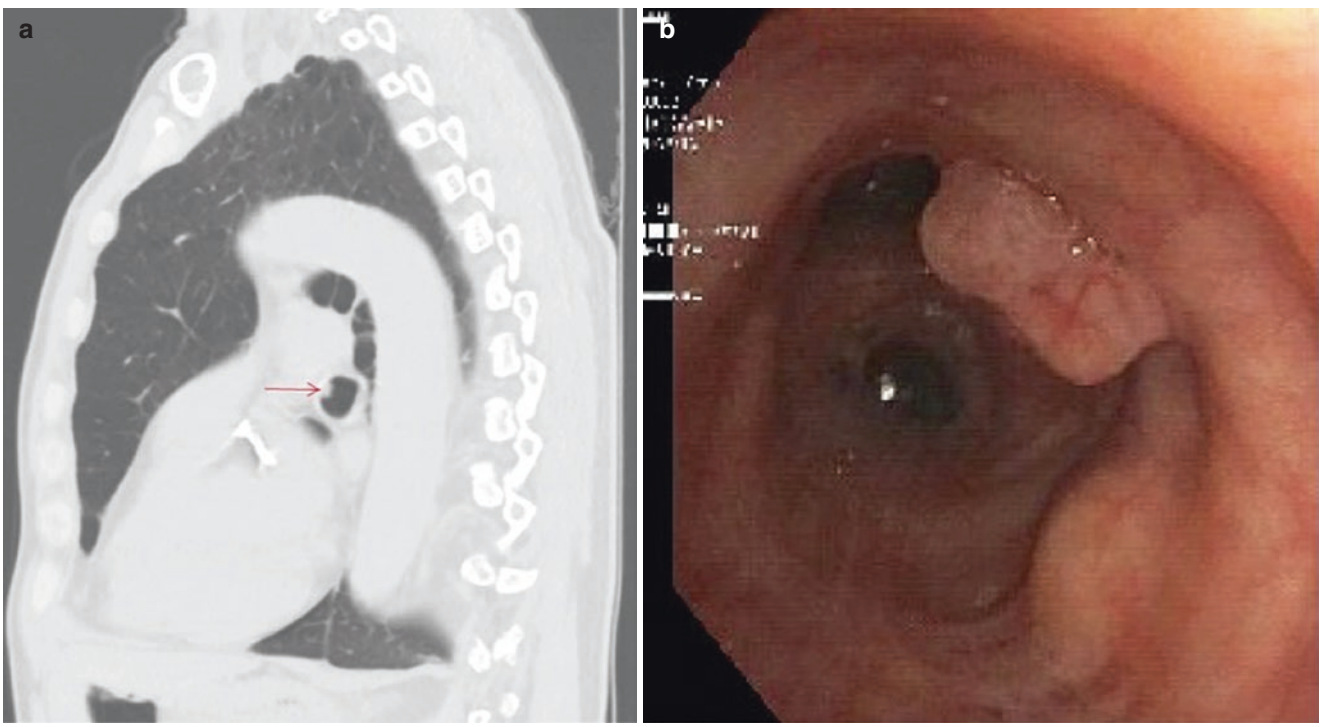

Fig. 15.4 61-year-old male with a new left mainstem sessile polyp on computed tomography of the chest (**a**, *arrow*). Prior history of pT1N1M0 squamous cell carcinoma of the oropharynx treated with surgery. Bronchoscopy revealed an endoluminal nodule and biopsy showed a non-small cell carcinoma with mucoepidermoid features (**b**). He underwent a thoracotomy with left mainstem sleeve resection

and an attempt to salvage contralateral lung are indications to intervene with therapeutic bronchoscopy, even when there is involvement of lobar bronchi (Fig. 15.7).

Management of massive or symptomatic hemoptysis is a harrowing clinical situation that can complicate MCAO. In symptomatic, alert patients maintaining their airway by coughing out blood, it is important to be completely prepared to assume control of the airway for intubation before paralyzing the patient as blood can quickly fill the trachea and mainstem bronchi leading to respiratory arrest. Visualization of the vocal cords can be difficult with direct laryngoscopy due to pooling of blood in the hypopharynx; video laryngoscopic and bronchoscopic visualization during intubation are useful adjuncts to secure an airway [22]. Tilting the patient toward the side of the bleed minimizes the blood flowing into the unaffected lung until the affected side can be isolated with an endobronchial blocker or contralateral mainstem intubation with a large endotracheal tube. If the cause of hemoptysis is known to be an endoluminal or mixed tumor and rigid bronchoscopy is readily available, the plan should be to proceed with rigid bronchoscopy as soon as possible. Bronchial artery embolization (BAE), a technique of selectively embolizing dilated or ecstatic bronchial arteries supplying tumors, must be considered if rigid bronchoscopy is not available, in cases of bleeding due to extraluminal

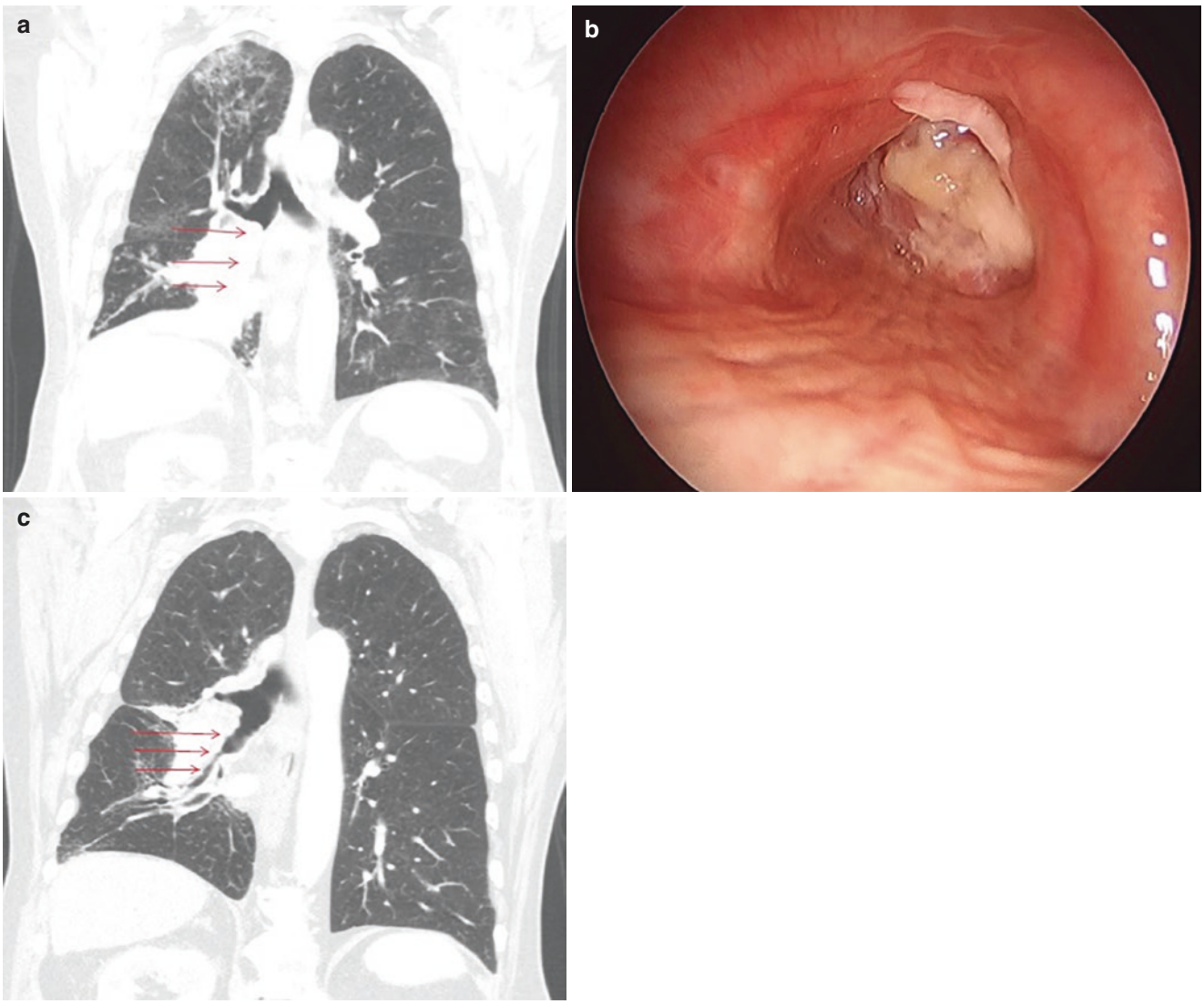

Fig. 15.6 73-year-old male with dyspnea and unresolving pneumonia of the right lower lobe. Computed tomography of the chest showed a mass in the right bronchus intermedius (**a**, *arrows*). Rigid bronchoscopy showed complete obstruction of the right bronchus intermedius with an endoluminal tumor (**b**). The right middle lobe and right lower lobe anterior segment were patent when the thin scope passed by the central tumor. The tumor was debulked with improvement in dyspnea and right lower lobe pneumonia, and he received definitive chemotherapy and radiotherapy to cT3N0M0 of the right bronchus intermedius. No evidence of recurrence 2 years after treatment on computed tomography of the chest (**c**; *arrows show patent right bronchus intermedius and radiation changes*)

MCAO or as a bridge to rigid bronchoscopy or surgery. BAE boasts high rates of immediate control of bleeding (>90%) [23, 24]. Recurrence after BAE occurs between 1% and 50% of cases and should be combined with definitive or palliative treatment of the underlying malignancy (surgery or radiation therapy) to prevent further episodes of hemoptysis [25]. Emergent surgical management of massive hemoptysis is associated with high mortality ranging from 15% to 25%. A single-center retrospective study of patients with massive hemoptysis showed that adopting BAE to control hemoptysis prior to surgery reduced mortality significantly [26]. Finally, the importance of correcting thrombocytopenia and coagulopathies as well as the reversal of antiplatelet agents and anticoagulants to control hemoptysis cannot be stressed enough.

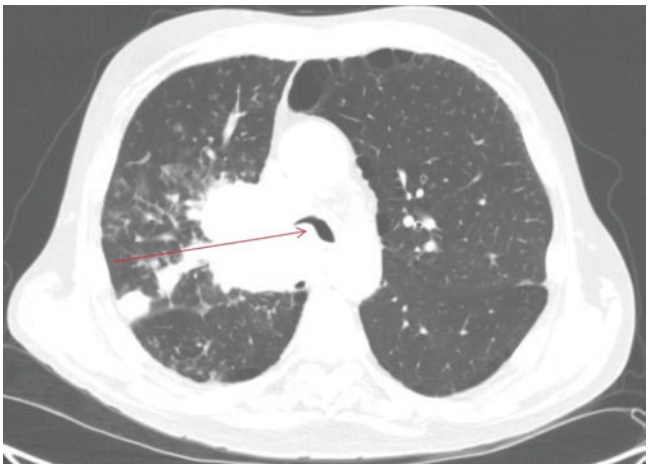

Fig. 15.7 Elderly male with an endoluminal squamous cell carcinoma, cT2aN2M0 of the right upper lobe extending slightly into the right mainstem presenting with large-volume hemoptysis. After rigid bronchoscopy, debulking, and cautery of the tumor, the patient declined all treatment options. He presented one year later with dyspnea due to tumor infiltration of right mainstem, right bronchus intermedius, and main carina with extension across the midline over the left mainstem. Post-obstructive pneumonitis seen in the right upper lobe distal to the large right hilar mass (shown in computed tomography of the chest). He underwent rigid bronchoscopy with successful recanalization of the right mainstem and right bronchus intermedius followed by palliation radiation to prevent obstruction of the left mainstem. He passed away one year later

Therapeutic Bronchoscopy: Tools

It is necessary to possess extensive knowledge about the unique characteristics of the tools used in therapeutic bronchoscopy to treat MCAO. Classic tools, such as the rigid bronchoscope, serve as foundational equipment through which interventions are performed safely. Other technologies have been adapted and customized for use in the airways from allied medical fields. The tools available can be classified into three broad categories: (i) mechanical tools, (ii) thermal tools, (iii) cold tools, and (iv) stents (Fig. 15.8).

Most MCAO require a variety of tools to reach the desired outcome of airway recanalization. To mitigate the perils of hemorrhage, endoluminal tumors are routinely cauterized prior to mechanical debulking or are debulked using tools that employ electrocautery. For extraluminal tumors, dilation followed by stenting is the only endoscopic method available to establish patency of the lumen.

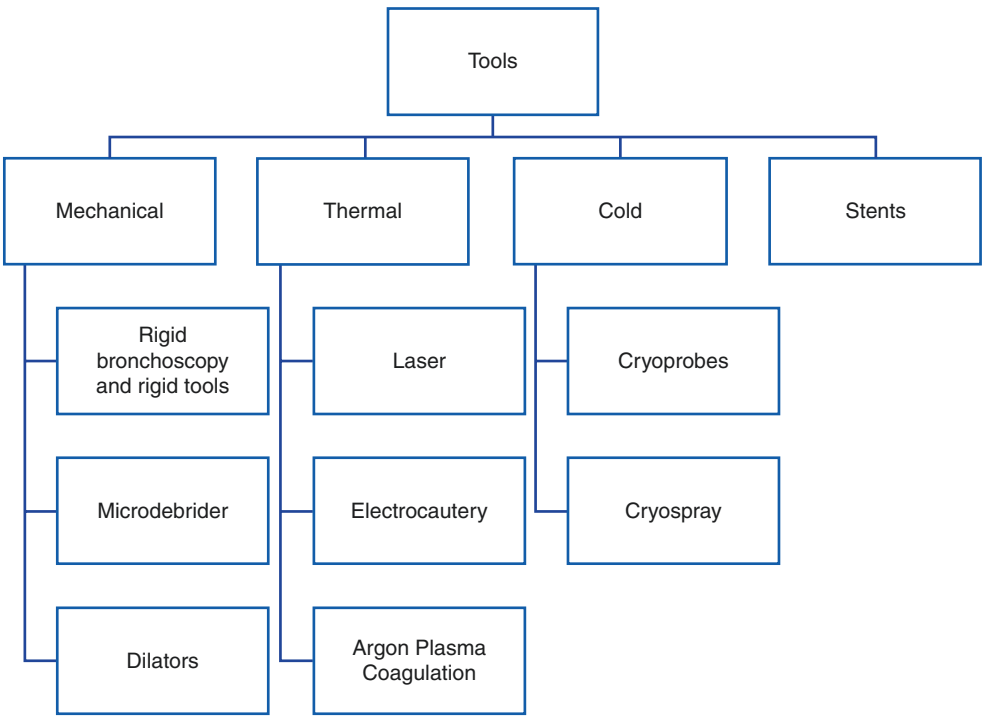

Fig. 15.8 Tools for therapeutic bronchoscopy

Mechanical Debulking

Mechanical debulking can be accomplished using a variety of rigid or flexible tools. The main advantage of this modality is that it allows rapid debulking without requiring a reduction in the fraction of inspired oxygen. This section will focus on a few prominent mechanical tools to address MCAO.

Rigid Bronchoscopy

Invented in the late 1800s to remove foreign bodies from airways, the rigid bronchoscope is now considered a fundamental tool for therapeutic airway interventions. The rigid bronchoscope has dual purposes. It is a straight, hollow, metal tube with a large lumen allowing the use of single or multiple, flexible, and rigid equipment. Additionally, the distal end of the bronchoscope has ventilatory side ports to allow ventilation while performing interventions. It is recommended to use the rigid bronchoscope for most therapeutic bronchoscopic interventions. The rigid bronchoscope is inserted into the airways under direct visualization with a rigid telescope. Some common methods of ventilation with the rigid bronchoscope include jet ventilation (manual or automatic, high or low frequency), spontaneous-assisted ventilation, and controlled mechanical ventilation [27]. The tip of the rigid bronchoscope is beveled and can also be used to "core" out endoluminal tumors. A variety of rigid instruments such as the rigid forceps, rigid electrocautery, rigid dilator, and high-volume suction catheter can be inserted through the rigid bronchoscope. The rigid scope also acts as the conduit for the microdebrider and insertion or removal of airway stents, which will be discussed later in this chapter.

Microdebrider

The microdebrider consists of a rotating cutting blade within a rigid metal suction catheter that is connected to a power console. The suction pulls tumor tissue into the rotating blade for resection and removes blood clots and debris out of the plane of view. The bronchial microdebrider blade can be used to resect tumors from the trachea and proximal mainstem bronchi with a high degree of success [28–33]. In skilled hands, complications are rare, but this device should be used cautiously as perforation of the airway walls and surrounding vascular structures could occur.

Dilators

Airway dilators can be rigid (used through a rigid bronchoscope) or flexible (disposable). Dilators are used to create a lumen in extrinsic compression (extraluminal or mixed airway obstruction) prior to deployment of a stent in MCAO. Radial expanding balloon dilators are available in many sizes and can be used with or without wire guidance through the working channel of a therapeutic flexible bronchoscope.

Thermal Tools

Thermal energy delivered through thermal tools, such as electrocautery, laser, and argon plasma coagulation, produce a variety of effects upon tissue based on the temperature generated by the instrument. Coagulation is useful both prior to debulking to devascularize tumors and after to control hemostasis at the base of the tumor. Temperatures must reach 60 °C at the tissue to produce a coagulation effect. For all thermal tools, there is a risk of an airway fire, so the fraction of inspired air should be less than 0.4 during application.

Laser

Lasers are used for their abilities to cut, coagulate, and vaporize tissue with each type of laser varying in its efficacy of these properties. The depth of penetration is determined by the laser beam's wavelength, distance from the tissue, and tissue absorbance. The neodymium-doped yttrium aluminum garnet (Nd:YAG) laser is most commonly used in MCAO management as it has excellent coagulation and ablative properties. Given the deeper penetration of lasers compared to other tools, there is an increased risk of airway perforation and fistula formation. A large retrospective case series reported success rates as high as 90% when recanalizing an obstructed airway using laser [34].

Electrocautery

Electrocautery utilizes heat that is generated when an electric current is met with resistance. A "coagulation current" is created when electricity is applied in alternating currents. This produces bursts of high-voltage peaks of energy resulting in thermal damage and coagulation. When a "cutting current" or

sinusoidal non-modulated waveform is used, it creates a higher average power that allows for smooth cutting and minimal thermal damage. A "blended current" alternates between cutting and coagulating currents. Given the heterogeneity of tissue composition – and subsequently its resistance – the effects of electrocautery can be unpredictable. Complications are rare but may include airway perforation, airway fire, airway stenosis, hemorrhage from damage to vascular structures and deprogramming of an implanted cardiac device. Newer high-frequency generators allow for more precise control of the power delivered and an automatic safety switch if temperatures reach 100 °C to prevent the formation of exploding steam pockets. A variety of electrocautery tools exist (e.g., rigid and flexible probes, snares, forceps). The tip of electrocautery tools must be cleaned frequently to maintain sufficient direct contact with tissue. Retrospective studies have shown good efficacy of electrocautery in the management of malignant and benign CAO, with the largest study reporting significant recanalization by bronchoscopic exam in 94% of cases and improved aeration on computed tomography in 63% of cases [35].

Argon Plasma Coagulation

Argon plasma coagulation (APC) is a type of noncontact monopolar electrosurgery used in the airways for over two decades [36, 37]. As argon gas passes by a high-frequency electrode, it is ionized into a plasma field between the electrode and nearby tissue leading to coagulation and desiccation. Different probe tips may direct the argon plasma flow forward, laterally or circumferentially. The effect on tissue can be modified by changing the gas flow rate, power, and mode of energy delivery. APC acts more superficially than other thermal therapies, and the resulting coagulated and desiccated tissue adds another layer of resistance in reaching the deeper, unaffected tissue. Although rare, APC can cause fatal gas embolisms particularly at higher flow rates and longer pulse durations [38].

Cold Tools

Cryotherapy: Cryoprobe and Cryospray

Certain gases (such as carbon dioxide and nitrous oxide) rapidly expand when moving from a high-pressure to low-pressure environment causing a drop in temperature. This is called the Joule-Thompson effect and is the basis of cryotherapy. Of the two modalities of cryotherapy available for bronchoscopy, the cryoprobe is the preferred method used to quickly reestablish patency of the lumen in acute symptomatic endoluminal or mixed MCAO. In cryo-recanalization, the tip of the cryoprobe is placed in contact with the tumor and activated to freeze the tissue until it is adherent to the probe. The tissue, probe, and bronchoscope are gently pulled away en bloc and removed from the airways without touching the airway walls. The advantage of this method is that it does not necessitate the reduction of fraction of inspired air in patients who are hypoxemic. Several prospective and observational studies have demonstrated a 77–94% success rate of relieving the obstruction by 50–100%. The most common complication seen in these studies was mild to moderate bleeding controlled with APC and/or electrocautery (4–10% of cases) [1, 39].

Cryospray or cryoprobe can be used to treat inoperable lung cancer of the airways or in situ lesions of the mucosa by applying repeat freeze-thaw cycles of extremely low temperatures (below −40 °C) to tissue, which results in direct cellular damage by the repeated intra- and extracellular crystallization of the water as well as dehydration of the tissue. The cold temperatures also cause tissue ischemia through vasoconstriction, formation of microthrombi, and increased blood viscosity. This method results in recanalization slowly and cannot be used to quickly relieve symptoms of acute MCAO.

Airway Stents

Airway stenting is a palliative procedure used to maintain patency of an obstructed airway. Airway stents are broadly classified as silastic/silicone stents or metallic stents, based on the composed material. Metallic stents (self-expanding metalic stent (SEMS) or balloon expanding) may be bare (no indication in MCAO) or covered (partially or completely with silicone or polyurethane to prevent tumor growth into the stent. Silicone stents are placed and removed through a rigid bronchoscope. Metallic stents can be placed through an endotracheal tube, but when doing so, the rigid bronchoscope should be easily available for removal if the stent is not deployed correctly. The optimal stent for MCAO fits perfectly along the airway wall and is neither too large (which can incite granulation tissue due to mucosal ischemia) nor too small (which increases the risk for migration). It completely covers the tumor and extends 0.5 cm proximal and distal to the obstruction [40].

There are only a few indications for airway stents in MCAO. Firstly, symptomatic extraluminal or mixed obstruction can be stented as a bridge to definitive or palliative therapy (Fig. 15.9). All forms of recurrent, symptomatic MCAO (endoluminal, extraluminal, or mixed) that have exhausted treatment options such as radiation or surgery can be considered for airway stenting. The benefit of airway stenting in asymptomatic patients with MCAO is not clear and should be assessed on an individual basis. Finally, placing an airway stent in tracheoesophageal fistulas with airway obstruction or excessive secretions can improve symptoms but should be performed only after considering esophageal stenting first.

Several large retrospective studies on the use of stents in malignant tracheobronchial central airway obstruction have

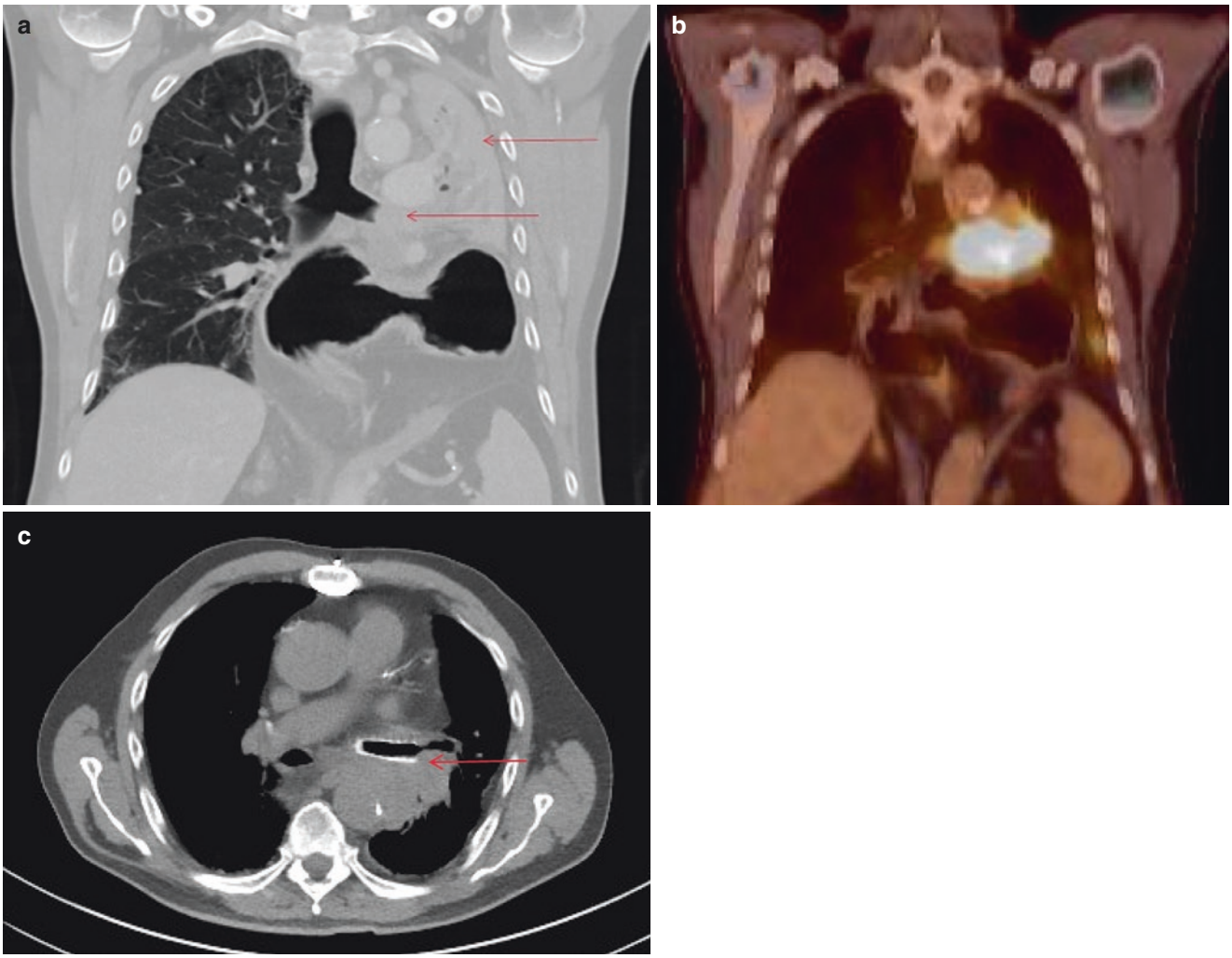

Fig. 15.9 70-year-old male with mild hemoptysis and dyspnea with exertion. Computed tomography and a positron emission tomography (PET) scan showed a large left infrahilar mass causing complete obstruction of left mainstem bronchus and collapse of the left upper and lower lobes (**a**, *arrows*), showing a large hiatal hernia that was chronic (**b**). Rigid bronchoscopy showed a mixed obstruction. The tumor was debulked, and a fully covered, self-expanding metallic stent was placed with resolution of dyspnea (**c**, *arrow*). Patient was treated with definitive chemotherapy and radiotherapy for a cT4N2M0 squamous cell carcinoma

reported on efficacy and safety of both silicone and self-expanding metallic stents but also focus on complications which include migration, obstruction from secretion, granulation, infections, and ulcerations [10, 41]. An absolute contraindication for airway stent placement is extrinsic compression from a vessel since the risk of erosion and development of a catastrophic fistula is extremely high. Overall, an airway stent is considered a useful adjunct for MCAO that must be used judiciously [42].

Conclusion

Malignant central airway obstruction can seriously impair quality of life and be life-threatening. Even in the most advanced malignancies, therapeutic bronchoscopy offers palliation of symptoms caused by MCAO. It is paramount to consider goals of intervention carefully, weighing risks and benefits with patient preferences for management. A multimodality and multidisciplinary approach to MCAO can both address the acute manifestations and provide long-term control.

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Central Nervous System

16

Prashant Rai, Akhil Shivaprasad, Ivo W. Tremont-Lukats, and Sudhakar Tummala

Introduction

In this chapter, we describe central nervous system (CNS) complications of cancer commonly presenting to the emergency department (ED), including altered mental status, high intracranial pressure/brain herniation, status epilepticus (convulsive and nonconvulsive), acute ischemic stroke, intracranial hemorrhage, and cerebral venous sinus thrombosis. We also briefly discuss the effects of SARS-CoV-2 on the CNS. Many patients present with more than one problem and more than one cause. This multiplicity can make diagnosis and management difficult. The goal is to preserve life and function, achieved by early, correct diagnosis. Still, patients come late in the disease course, or these neurological emergencies unfold quickly and catastrophically. Acute mental status change is the top neurological symptom in cancer patients; it is the final common path to intracranial hypertension, epileptic seizures, infection, electrolyte abnormalities, intracranial hemorrhage, ischemic stroke, and adverse effects from drugs. The emergency physician should also be comfortable in starting discussions on goals of care and advance care planning before admission to other hospital areas.

Approach to the Patient with Altered Mental Status

Mental status is a state of wakefulness in alert persons. Changes in mental status can also affect cognition, including orientation to self, place, and time; the ability to register and recall objects (memory registration and recall after minutes); and the ability to understand and execute more complex commands, such as backward spelling or arithmetic operations (attention/concentration) and language.

Changes in mental status can occur in a patient with normal mental function or can appear against the backdrop of a chronic cognitive disorder such as dementia or mental retardation. In the medical literature, the terms altered mental status, changes in mental status, confusion, encephalopathy, and delirium are often used interchangeably. Encephalopathy and delirium are more relevant as diagnostic keywords. For simplicity, we will use delirium in this chapter for any acute change in arousal and mental function.

Frequency and Importance

In cancer, delirium is a life-threatening complication and a powerful driver of emergency services. Care providers in the ED frequently overlook delirium, with a reported misdiagnosis rate of 41% in the ED of an NCI-designated comprehensive cancer center [1, 2]. Its frequency ranges from 57 to 85% in cancer patients compared to 15–30% in medically ill hospitalized patients [3]. Among 352 cancer patients in the acute palliative care unit at The University of Texas MD Anderson Cancer Center, delirium was the most common diagnosis in 43% at admission, increasing to 70% during the entire stay [4]. At Memorial Sloan Kettering Cancer Center (MSKCC), delirium accounted for 27% of all inpatient neurology consults. This figure did not include psychiatry consults or unrecognized cases [3]. A review of 771 inpatient palliative care consults found that referring teams missed the

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diagnosis in 61% of cases, of which 63% had hypoactive delirium [2].

Causes

Many patients with cancer have more than one reason for delirium [5, 6]. The most important causes in the ED are illustrated in Fig. 16.1. The first three suspects to investigate are drugs, sepsis, and organ failure [6]. Opioids and benzodiazepines are the most common drugs causing delirium in the ED, in surgical recovery rooms, and during hospitalization. It is impossible to quantify the relative weight of each drug in cases of polypharmacy, especially when accompanied by renal or liver impairment and advanced age [7].

The worldwide emergence of coronavirus disease (COVID-19) due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with higher mortality rates in cancer patients [8, 9]. A surveillance study in the UK reported AMS as the second most common neurologic complication in COVID-19, in 31% of 125 cases [10]. We currently do not have longitudinal data mature enough to estimate the frequency, course, and prognosis of delirium from COVID-19 in cancer, or whether it is from neuroinvasion, hypoxia, or both [11, 12]. The current view is that the COVID-19-related encephalopathy is the result of age, comorbidities, and the systemic inflammatory response to the infection, including adult respiratory distress syndrome (ARDS) resulting in cerebral hypoxia in postmortem examination [12, 13]. Preliminary evidence in non-cancer patients admitted to intensive care units with ARDS showed that, in addition to other neurologic findings, delirium was frequent (65%). Approximately 33% of survivors remained disoriented and inattentive after discharge [14].

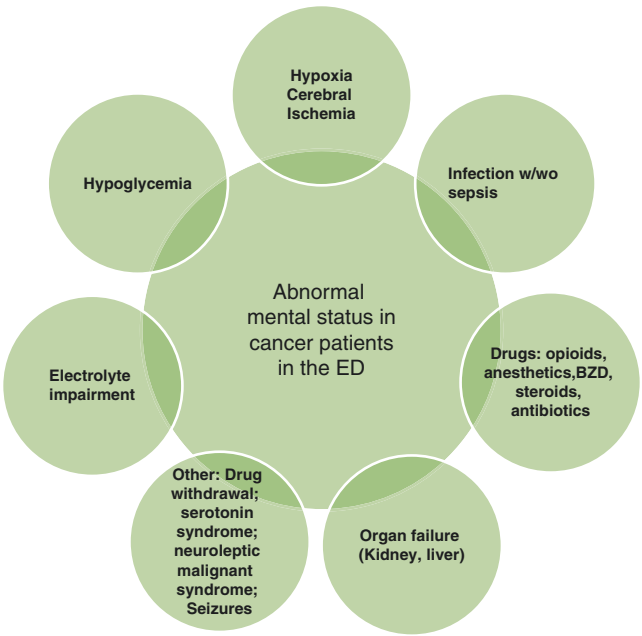

Fig. 16.1 Causes of abnormal mental status of patients in the emergency department. *BZD* Benzodiazepines; *ED* Emergency Department

A long list of chemotherapy agents, immune checkpoint inhibitors (ICI), and chimeric antigen receptor (CAR) T-cell therapies can also cause central neurotoxicity (Table 16.1) [15–17]. The immune-effector cell-associated neurological syndrome (ICANS) is a distinct, common complication of adoptive T-cell immunotherapy [18]. Some of these drugs have been linked to the posterior reversible encephalopathy syndrome (PRES). Physicians caring for cancer patients in the ED should consider PRES if symptoms and findings (confusion, headaches, cortical blindness, seizures, and hypertension) suggest the diagnosis and patients are on chemotherapy or immunosuppressive drugs [19, 20]. Another cause is progressive multifocal leukoencephalopathy (PML) among leukemia and lymphoma patients treated with monoclonal antibodies targeting B and T cells. Delirium is also one of the complications of allogeneic HSCT due to chronic immunosuppression for the prevention of graft versus host disease [21].

Diagnosis

Two elements are essential to the diagnosis of delirium: (1) acute or subacute onset in minutes, hours, or even a few days and (2) fluctuation in attention levels.

There are several instruments for the assessment of mental status in cancer patients [56]. The mini-mental state examination (MMSE) is easy to learn and use. It can detect encephalopathy within 1 minute, especially when assessing orientation, recall, and attention/concentration [57]. The language domain is generally unremarkable in mild or moderate delirium. The MMSE is useful to evaluate and diagnose delirium in patients with baseline dementia, but it is not adequate to screen for dementia itself. In the ED, pre-existing dementia is often based on information on prior cognitive function from relatives or friends.

Assessment and Management

Not every patient needs all the tests in Fig. 16.2. The essential laboratory data and procedures for adequate diagnosis of encephalopathy and its cause(s) are contained in the two upper bullets of the diagram. The treatment of delirium is supportive, and its resolution depends on control of the underlying problems; if these complications resolve, encephalopathy should improve. Figure 16.3 depicts the principles of treatment, as reviewed in detail elsewhere [7].

Table 16.1 Chemotherapy and other anticancer drugs associated with encephalopathy/delirium

Drug	Frequency	Comments
Bevacizumab	Unknown	Associated as monotherapy, or with other drugs in PRES [19, 22, 23]
Bortezomib and carfilzomib	Unknown	Well-known association with PRES [24, 25]
Blinatumomab	All grades: 36–53% ≥ grade 3: 7–14%	Pooled data [26, 27]
CAR T-cell therapy: Axicabtagene ciloleucel (YESCARTA®) Tisagenlecleucel (Kymriah®) Brexucabtagene autoleucel (Tecartus®)	ICANS (any grade): 68% [28] ≥ grade 3: 30–41% [28–30]	Stereotypical presentation, biphasic pattern. Early: tremor, dysgraphia, aphasia. Aphasia can be prominent later and is very specific for this class [18]. PRES in 2% [28]
Cisplatin	Unknown but rare	Described with PRES
Etoposide	Unknown but rare	Described with PRES
Fludarabine	Very rare but serious	
5-Fluorouracil	Very rare	Check for dihydropyrimidine dehydrogenase (DPD) deficiency
Gemcitabine		
Ifosfamide	15–21% [31, 32]	Risk is higher in ECOG PS 2–4, and increase in serum creatinine levels [33]
Interferons (**α** and **β**)	Rare, discrepant reports on severity [34, 35]	No association with PRES
Interleukin-2	Rare [36–38]	
Ipilimumab	<1% [39]	Described with PRES [40]
L-Asparaginase	Unknown, case reports [41]	Mostly during consolidation associated with PRES [42]
Methotrexate	With sporadic reports since the 1970s, frequency unknown	Described with parenteral [43–45] and intraventricular administration [46–48] associated with PRES [49]
Nitrosoureas	Unknown	Causality is difficult to demonstrate because the current use of these drugs is to treat CNS tumors
Procarbazine	Unknown; association is very weak	Described with CCNU and vincristine [50], not in PRES
Sunitinib	Unknown	Associated with PRES [51]
Tamoxifen	No firm association [52]	Not described in PRES
Thiotepa	18% with high-dose regimens [53]	Use of tramadol may increase the risk of neurotoxicity
Vincristine	Unknown	Causality unclear, associated with PRES [54, 55]

CAR T Chimeric antigen receptor T-cell therapy, *PRES* posterior reversible encephalopathy syndrome, *ICANS* immune-effector cell-associated neurological syndrome, *ECOG* Eastern Cooperative Oncologic Group, *PS* performance status

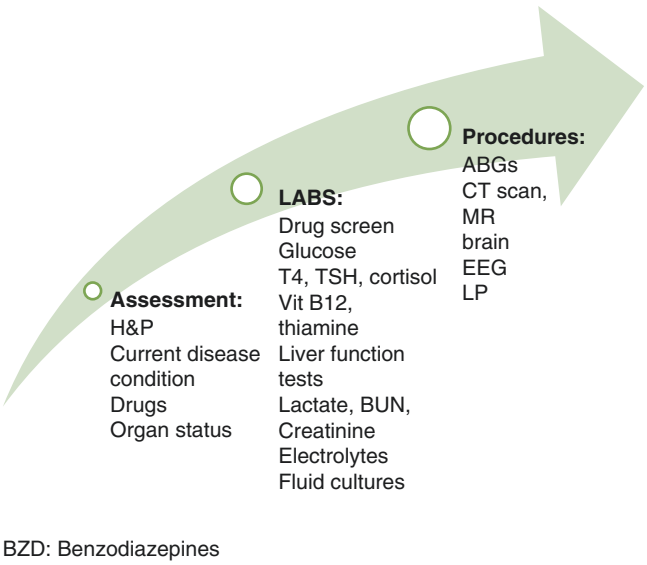

Fig. 16.2 Diagnostic sequence in the diagnosis of altered mental status (ABG arterial blood gases, EEG electroencephalogram, LP lumbar puncture)

Brain Herniation

Principles

Intracranial volume is the sum of the volumes of brain tissue, cerebrospinal fluid (CSF), and blood, within a rigid compartment (skull) [58]. This means that changes in relative volumes will not alter the total intracranial volume (Monro-Kellie doctrine). Figure 16.4 illustrates the interplay among these compartments and how an increase in intracranial pressure (ICP) can lead to brain herniation. High ICP triggers a compensatory shift of CSF into the spinal subarachnoid space and a reduction of blood volume by the cerebral venous system. If the cause of high ICP supersedes these homeostatic mechanisms, ICP will rise, and the brain parenchyma can herniate in three directions following a gradient pressure: under the falx (subfalcine herniation); past the tentorium cerebellum (uncal or transtentorial herniation); and past the foramen magnum (tonsillar herniation) [59]. Early recognition of impending

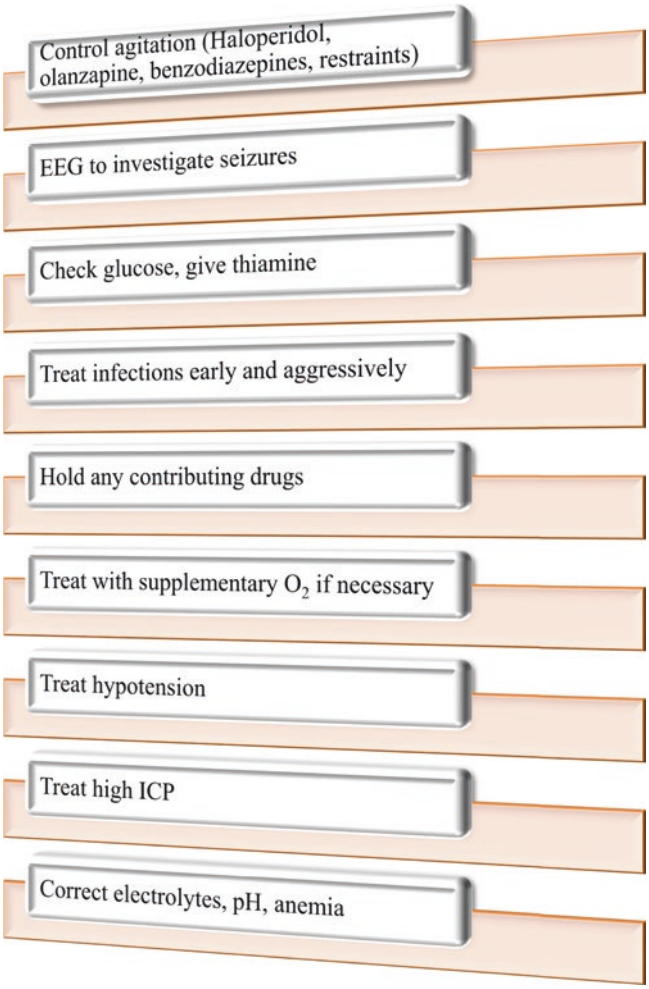

Fig. 16.3 Emergency department management of altered mental status in cancer patients

brain herniation will allow prompt treatment (Fig. 16.5). Miller Fisher argued that the crucial and irreversible injury are the events preceding herniation, such as displacement of midline structures against the tentorium or overcrowding of the posterior fossa [60], and this is supported by clinical observations [61].

Causes

In oncologic practice, cerebral edema and an intracranial mass are the most common causes of brain herniation syndromes. The intracranial mass can be (1) a primary tumor (e.g., glioblastoma, meningioma with brain invasion, or ependymomas); (2) a brain metastasis (single or multiple); and (3) radiation necrosis. In these cases, the perilesional edema is from BBB disruption (vasogenic) and can respond to corticosteroids.

Alternatively, nontumoral lesions with focal mass effects may cause intracellular (cytotoxic) edema unresponsive to steroids. Causes include (1) hypertensive hematomas; (2) traumatic or non-traumatic intracranial hemorrhage; (3) ischemic infarcts in the distribution of a large vessel such as the carotid artery or main trunk of the middle cerebral artery (MCA); and (4) vasculitis (if ischemia or hemorrhage predominates and the vasculitis is not due to an autoimmune process).

A third group has high ICP with diffuse cerebral cytotoxic edema from widespread cellular injury and includes the following: (1) hypoxia from cardiorespiratory arrest; (2) refractory convulsive epileptic status; (3) liver or renal failure; and (4) hydrocephalus (in neoplastic meningitis).

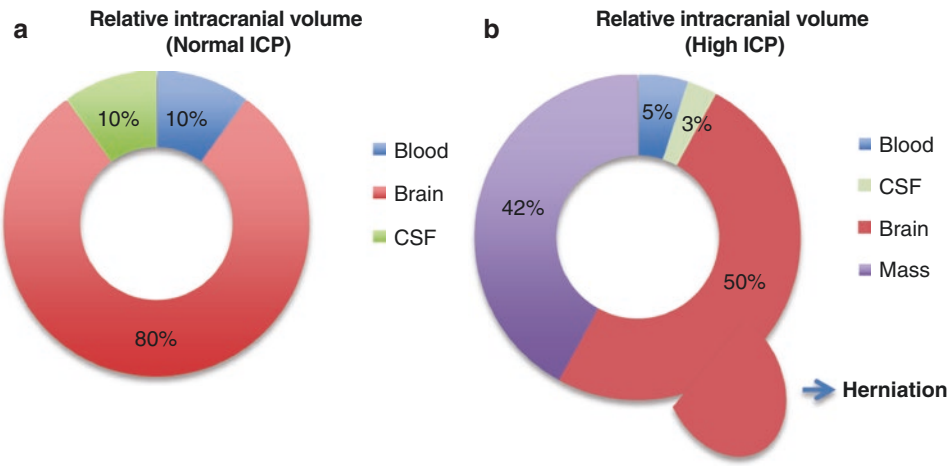

Fig. 16.4 Relative intracranial volume. (**a**) Normal intracranial volume pressure (ICP), (**b**) relative ICP (CSF, cerebrospinal fluid)

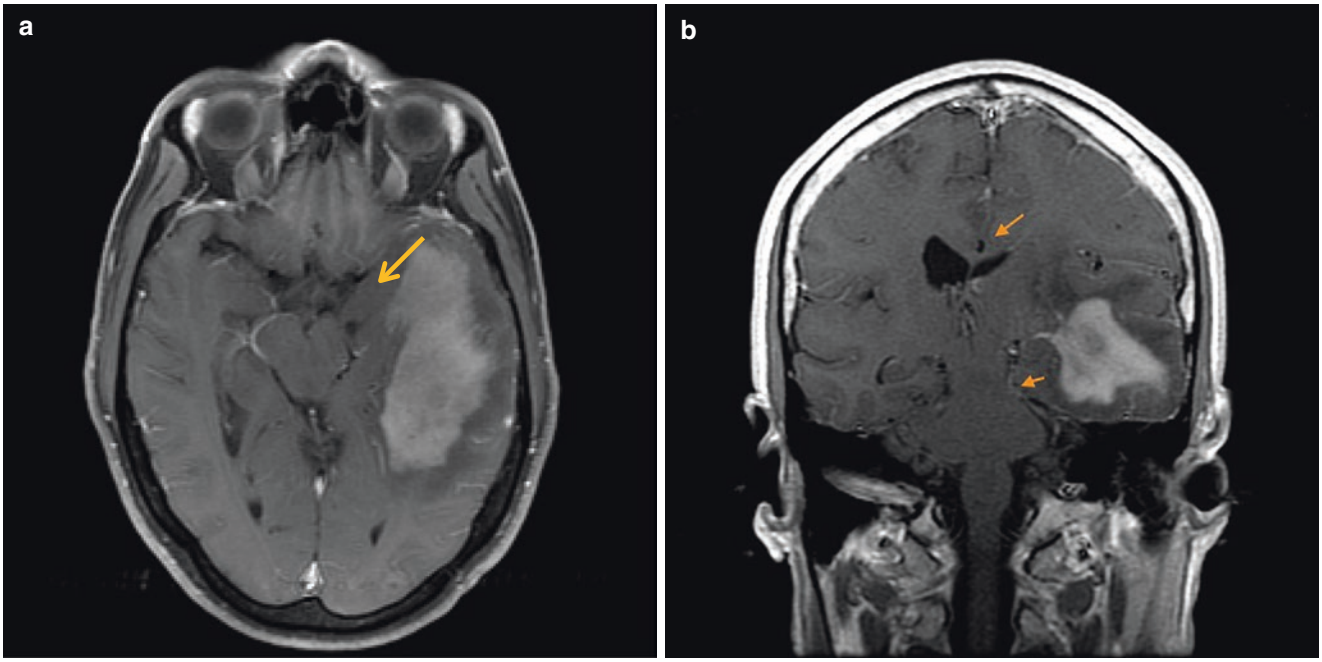

Fig. 16.5 Patient with metastatic B-cell lymphoma. (**a**) T1-gadolinium axial MRI. The left uncus is shifting against the cerebral peduncle (impending uncal herniation). (**b**) MRI of the brain, T1 with gadolinium, coronal section. Another view of the uncal displacement (*straight arrow*) and a simultaneous subfalcine herniation

Assessment

Not all patients with intracranial hypertension present with the same symptoms and findings; we have seen patients with radiographic evidence of impending herniation but a normal neurological examination, although they are rare (<5%) [62]. Many others do not have herniation but a mass effect, neurological deficits, and AMS. In general, headache, neck pain, AMS, or seizures can indicate high ICP. Papilledema is a useful sign with low sensitivity, and very few physicians in the ED have funduscopy skills to identify papilledema (Fig. 16.6). Point of care ultrasound may be a useful adjunct to fundoscopy in making the diagnosis of intracranial hypertension [63].

Other patients can present with acute bursts of neurologic dysfunction, often mistaken for epileptic seizures; many of them have mass lesions or hydrocephalus from leptomeningeal involvement. Such episodes are due to a sudden rise in intracranial pressure (plateau waves) and last from 1 to 20 min (Table 16.2). The EEG can sometimes show indirect clues of increased ICP with frontal intermittent rhythmic delta activity (FIRDA) patterns (Fig. 16.7).

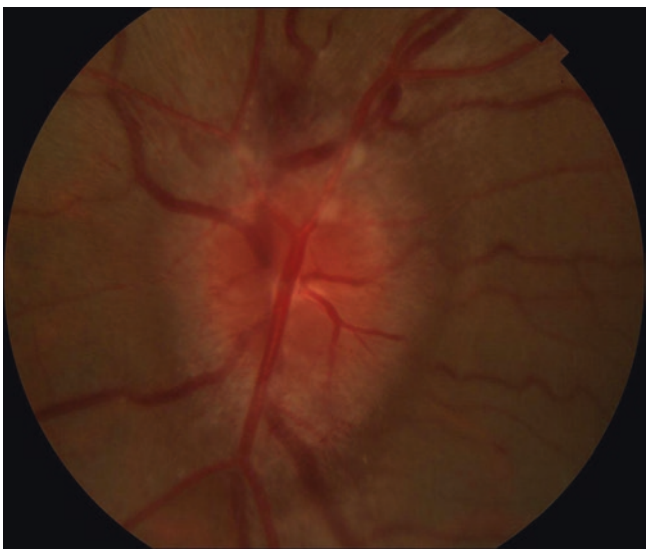

Fig. 16.6 Papilledema in a 53-year-old woman in the ED with new onset, daily headaches. Bedside fundoscopy quickly established a secondary headache. Opening cerebrospinal fluid pressure: 40 cm H20. Cytology: adenocarcinoma cells. Blurred optic disc contours, blurred retinal vessel walls, and soft exudates

Management and Prognosis

After an ED diagnosis of high ICP with or without evidence (clinical or radiographic) of brain herniation, the specific circumstance will dictate the urgency of treatment. The choice of medical interventions depends on the cause responsible for high ICP, and these include hyperventilation, osmotherapy, and corticosteroids (Table 16.3). Hyperventilation can be started in the ED,

with advanced airway management and mechanical ventilation before transfer to intensive care. Mannitol and corticosteroids can begin in the ED and continue on the hospital floor. Most hypertonic saline infusions, particularly 7.5%, 15%, and 23.4% sodium chloride, require ICU monitoring. The prognosis of symptomatic, acute brain herniation in cancer patients is dismal, with most dying in minutes or hours regardless of the cause. Even if they survive resuscitation efforts, they will remain unresponsive and comatose until death. Patients with metastatic or primary brain tumors and gradual elevation of ICP are more likely to respond to osmotherapy, steroids, and debulking surgery, if indicated.

Table 16.2 Signs and symptoms associated with plateau waves [5]

Altered consciousness (delirium, stupor, or coma)
"Spells" of blank stare (confused with partial complex seizures)
Spontaneous, wide oscillations of blood pressure, respiration, or heart rate
Headache, pain in neck or shoulders
Nasal pruritus
Nausea/vomiting
Facial flushing
Shivering, goosebumps, sweating
Temperature increase
Yawning or hiccups
Opisthotonus
Mydriasis
Weakness of cranial nerve III or VI
Nuchal rigidity
Clonic movements of extremities
Decorticate or decerebrate posturing
Bilateral extensor plantar signs

These episodes are paroxysmal, may last minutes, and may be triggered by touch, pain, suction, positioning, or noise

Status Epilepticus (SE)

Definition and Classification

Status epilepticus can be convulsive (CSE) or nonconvulsive (NCSE), and patients can evolve from one to another in the ED. CSE is easily recognizable, with partial (focal) tonic-clonic, generalized tonic-clonic, or predominant tonic posturing or clonic movements (rhythmic jerking), or mixed. Convulsive status epilepticus (CSE) is a life-threatening emergency [65].

Status epilepticus from some regions of the brain (temporal lobe, occipital and deep frontal) might not have overt motor manifestations and typify a complex partial status epilepticus. These events require observation of subtle movements or behavioral changes by observant witnesses or care providers:

- Licking behavior
- Lip-smacking
- Chewing, tooth grinding, spitting
- Grunting or guttural sounds
- Aversive or versive eye/head movements
- Nystagmus
- Myoclonus of eyelids, face, or perioral regions
- Picking/fumbling, facial grimacing, gesticulating activity
- Isolated focal facial, finger, or toe twitching

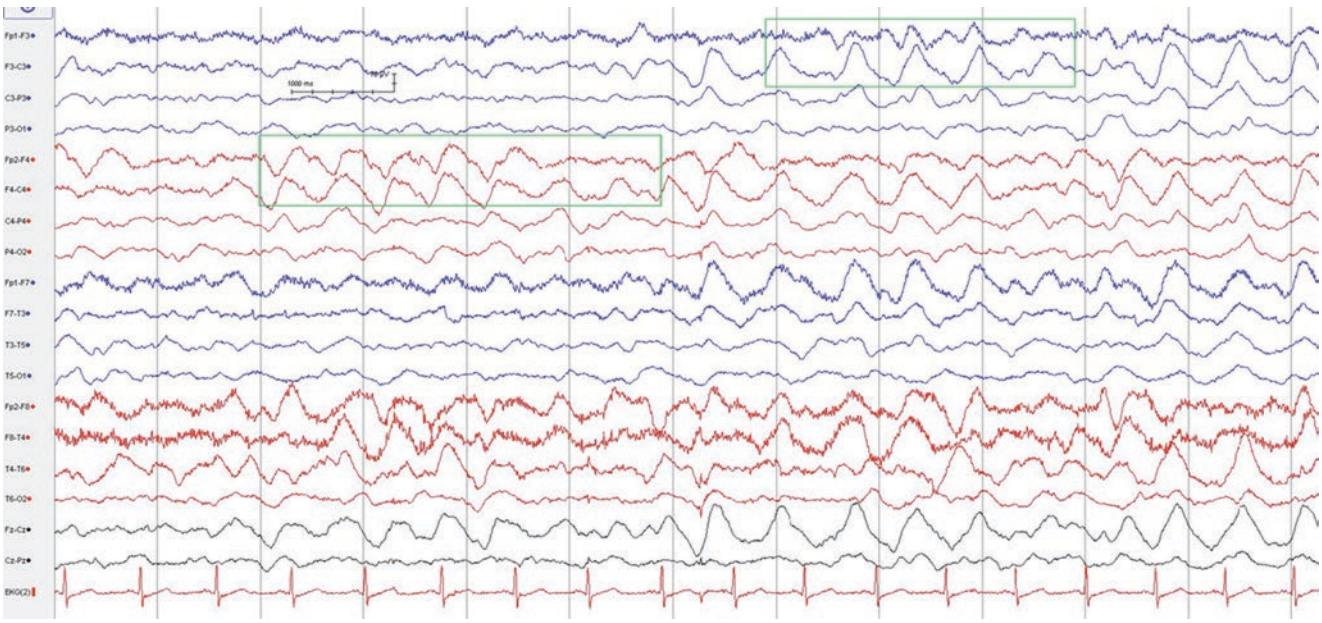

Fig. 16.7 Frontal dysfunction with delta (FIRDA, *boxes*). Opening cerebrospinal fluid pressure: 27 cm H2O. Patient with plateau waves

Table 16.3 Emergency medical treatment of patients with de facto or impending cerebral herniation [28]

Intervention	Dose	Onset/duration	Advantage(s)	Disadvantage(s)
Hyperventilation	Lower pCO2 to 25–30 mmHg by increasing respiratory rate with same tidal volume	Seconds/minutes	Fastest onset Effective for high ICP regardless of the cause	Very short duration, with effect lost after several hours Will require endotracheal intubation May be more harmful to an already injured brain
Osmotherapy (mannitol, 20% solution)	1 g/kg iv initial dose; next dose: 0.5 g/kg and 0.25 g/kg q6h	Within 15–20 min; max effect is in 1 h Keep osmolality between 210 and 320 mOsm/L	Longer duration Effective regardless of the cause Note: still is the standard of care in cancer patients	Rebound effect is possible Hyperosmolality and acute renal failure
Osmotherapy (hypertonic saline solutions)	3%: 250 mL 7.5%: 250 mL 23.4%: 30–60 mL	Onset: within min	Effective when mannitol is not Needs central line for administration – could be considered for rapidly evolving herniation	Minimal experience in brain tumors Safer than mannitol but it may have adverse effects: CHF, hyperchloremic acidemia, hypernatremia, seizures
Corticosteroids (dexamethasone most used)	Initial dose: 10 mg, then 4–6 mg iv q4–6 h. Decrease as soon as possible	24–36 h/days	Reliable and steady effect in vasogenic edema from metastatic or primary brain tumors	Not effective in anoxic-ischemic or toxic edema AE: hyperglycemia, mood changes, insomnia, immunosuppression, Cushing syndrome, skin frailty, accelerated bone resorption Myopathy can be disabling

ICP Intracranial pressure; *CHF* congestive heart failure; *AE* adverse effect

- Pelvic thrusting and bicycling movements
- Asymmetric tonic posturing ("sign of four")
- Dystonic limb posturing

These symptoms and signs require bedside EEG for prompt diagnosis. NCSE also presents with AMS and behavior changes from baseline, without overt motor manifestations. The list is diverse and includes:

- Altered consciousness
- Impairment of verbal skills
- Impairment of clock drawing
- Indifferent attitude
- Fear
- Rare hysteria
- Suicidal thoughts
- Hallucinations

Bedside EEG is essential for prompt diagnosis. Status epilepticus involves ongoing or recurrent seizures *without* recovery of sensory, motor, or cognitive function or consciousness to baseline. The duration of seizures in the definition of CSE has changed over time from 30 min to 5 min; we consider seizures lasting 2 minutes or longer in cancer patients as an emergency requiring prompt treatment and workup. There is no consensus on how soon to intervene; other experts recommend treatment after 5 min [64].

Unlike CSE, NCSE requires timely recognition without overly aggressive treatments. NCSE has a prevalence of 15% among critically ill cancer patients and seems associated with lower mortality, normal kidney function, and hematologic malignancies receiving chemotherapy [66]. Postictal deficits (Todd paralysis) include temporary limb weakness or hemiplegia after a seizure, with new or worsening of prior known weakness, and clinically masquerade as an ongoing seizure. The EEG is necessary to identify surreptitious seizure activity.

Causes

Epileptic seizures are a frequent symptom of CNS metastases (leptomeningeal, dural, or parenchymal), primary brain tumors (meningiomas, astrocytomas, and oligodendrogliomas, with oligodendrogliomas having the highest seizure rate), metabolic disorders (hyponatremia, hypoglycemia, hypoxia, and hypercalcemia), CNS infections (herpesvirus), intracranial hemorrhage (spontaneous or traumatic), ischemic infarctions, and treatment-related factors, as well as paraneoplastic limbic encephalitis.

In the era of immunotherapy, we increasingly recognize autoimmune encephalitis, meningitis, and demyelinating brain lesions. We also see seizures associated with blinatumomab and CAR T-cell therapy. If these patients return to the ED with AMS, it is necessary to perform a complete workup (sepsis workup, MR brain, EEG, lumbar puncture).

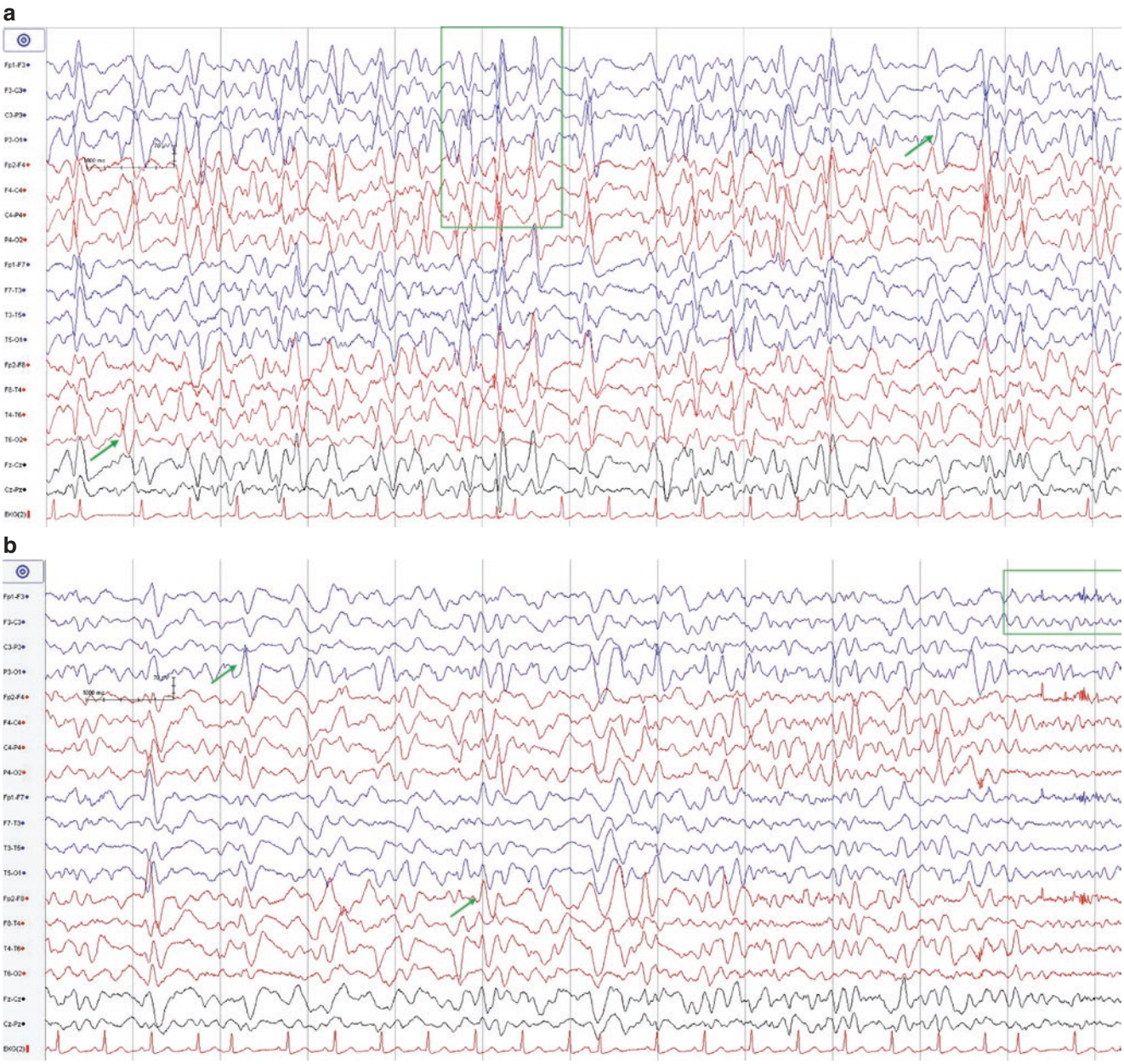

Fig. 16.8 (**a**) Nonconvulsive convulsive status epilepticus with ifosfamide toxicity: disorganized background with generalized and multifocal periodic complexes that are isolated (*arrow*) and at 2.5 Hz (*box*). (**b**) After 1.5 mg lorazepam: organized background (*box*) with attenuation of the periodic complexes (*arrow*). Patient able to state her name and follow one-step commands. Normal MR brain

Assessment

ED providers should observe or inquire for behavior changes, subtle movements, and AMS. Manifestations of NCSE can range from being awake, able to count from 1 to 20 but not backward, to confusion and overt coma. Clinical and EEG improvement to a benzodiazepine challenge (Fig. 16.8) can facilitate the diagnosis. The EEG has limitations, especially with intermittent seizures. Prolonged EEG or repeat EEG can increase the detection level, and a nondiagnostic EEG does *not* rule out a seizure. Clinical judgment should prevail, acknowledging the limits of diagnostic tests, and with high suspicion it is clinically and ethically justified to start benzodiazepines and anticonvulsant drugs [67], and we recommend upfront treatment if EEG is not readily available. An EEG should be performed following resolution of CSE if the patient's mental status and focal neurological deficits have not recovered to baseline. The aim is to rule out subclinical electrographic seizures.

Management and Prognosis

The initial assessment and treatment of CSE is detailed in Fig. 16.9. After securing ventilatory and circulatory support, the early and rapid use of benzodiazepines, phenytoin, levetiracetam, lacosamide, sodium valproate, phenobarbital, propofol, midazolam, and, in some cases, pentobarbital may prevent progression to refractory and super-refractory status epilepticus. Any seizure longer than 2 minutes should be treated aggressively. If the duration is uncertain, treatment has to be equally aggressive, even though the probability of success ("breaking" the SE) is less if the patient has been in status for hours or days. The prognosis is complicated and depends on the duration of status, underlying causes, and presence of additional complications. CSE and partial status epilepticus can contribute to further neurological injury in cancer patients due to cytotoxic edema and intracranial hypertension.

NCSE generally requires 1 to 4 mg lorazepam in different doses and sequences, for example, 1 mg doses as needed with reassessments in between or 2 mg plus additional doses as needed. Drugs with little or no sedating effects (levetiracetam or lacosamide) are preferred.

Following the resolution of NCSE, we recommend lower-dose intermittent lorazepam 0.5 mg iv q4–8 hrs x 24 hrs. Follow-up EEGs can often be indeterminate with trials of benzodiazepine and antiepileptic drugs.

NCSE and CSE share similar etiologies, and it is essential to address the root cause quickly. In our experience, leptomeningeal disease, drugs (ifosfamide, cephalosporins), and acute or acute-on-chronic renal injury are among the most common reasons. For both conditions, clinical improvement and EEG (Fig. 16.8b) are therapeutic endpoints.

Intracranial Hemorrhage (ICH)

Importance and Causes

Although the overall incidence is unknown, ICH is a frequent ED diagnosis in any institution caring for patients with cancer. ICH is a generic term that includes parenchymal, subarachnoid, subdural, and epidural hemorrhage. Although non-traumatic, ICH can occur as an adverse effect of supratherapeutic anticoagulation (but not therapeutic anticoagulation for venous thromboembolic disease [68]) or due to profound or prolonged

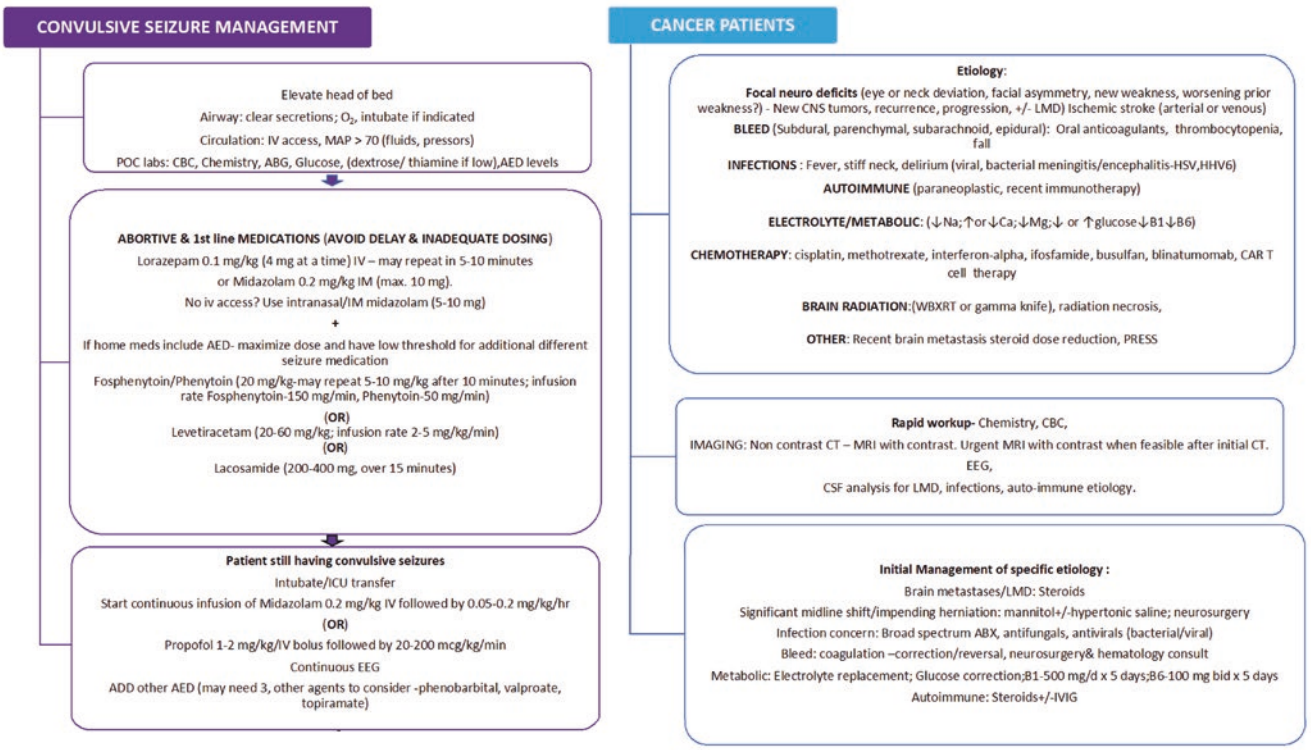

Fig. 16.9 Management guidelines for convulsive status epilepticus in cancer patients at the University of Texas MD Anderson Cancer Center. MAP Mean arterial pressure, POC point-of-care, CBC complete blood count, ABG arterial blood gases, AED antiepileptic drugs, LMD leptomeningeal disease, WBXRT whole brain radiation therapy, SRT stereotactic radiotherapy, ABX antibiotics, IVIG intravenous immunoglobulin

thrombocytopenia caused by drugs, disseminated intravascular coagulation (DIC) [69], or sepsis.

In solid tumors, bleeding can be spontaneous because of neovascularization (melanoma, lung cancer, renal cell carcinoma, or glioblastoma). ICH is an adverse effect with bevacizumab, but there is no evidence of additional risk in these patients [70]. The 72 h mortality rate of ICH in leukemia ranges between 12% and 19%. After 30 days, it climbs up to 40% [71]. Old age and high disease burden increase the risk of death [69].

Presentation

Patients with ICH can present with symptoms ranging from an incidental finding on CT scan of the brain to the classic picture of sudden headache, AMS (including stupor and coma), focal deficits, and epileptic seizures. Incidental or mildly asymptomatic presentations are more frequent in patients with intratumoral bleeding. Patients without a history of cancer may present with an ICH as the initial manifestation of neoplasm.

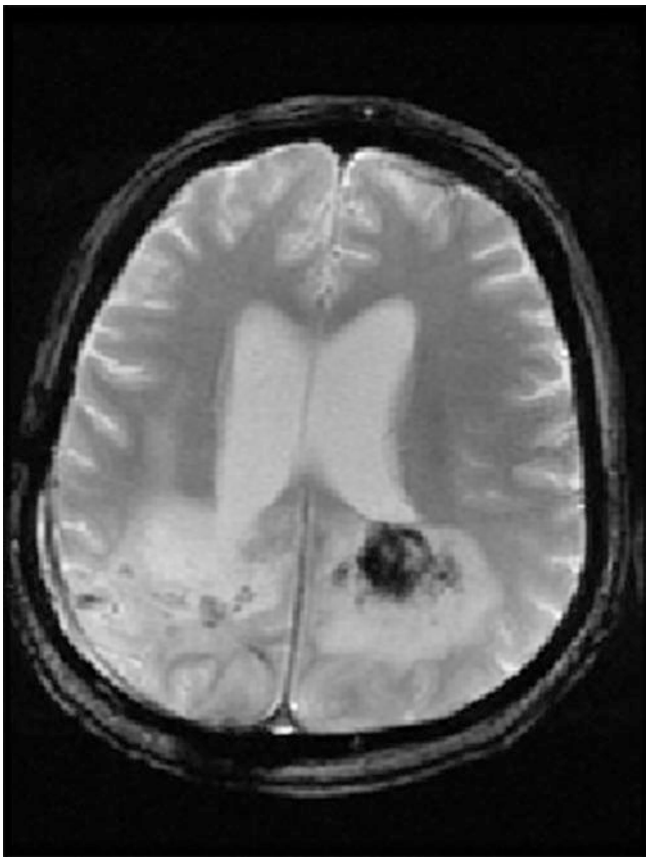

Fig. 16.10 Intratumoral hemorrhage in glioblastoma. Axial T2* MRI of the brain of a 49-year-old man presenting with a 7-day history of confusion. Fluent (Wernicke-type) aphasia on exam. No headaches

Diagnosis

A CT scan confirms ICH in most cases. In doubt, the MR brain with T1 with/without gadolinium and gradient echo or T2* (star) sequences are most helpful (Fig. 16.10). Bleeding in venous angiomas, cavernomas, incidental aneurysms, and elderly patients with amyloid angiopathy can sometimes pose a problem of differential diagnosis. In most cases, a careful analysis of the MRI sequences correctly identifies the cause.

Treatment and Prognosis (Fig. 16.11)

The treatment of ICH depends on the location of bleeding and cancer status. For prognosis, see section "Importance and Causes" above. Aggressive platelet and factor transfusion is indicated with the goals to keep fibrinogen >150 mg/dl and platelets >50 × 10^9 L^{-1}. Most patients with solid tumors and ICH that are symptomatic but stable can be managed conservatively. Critically ill patients usually arrive after cardiac arrest or are stuporous or comatose. These patients, if they survive, have severe and irreversible neurological deficits that will exclude them from further oncologic interventions, and supportive care is the best option.

Acute Ischemic Stroke

Importance and Causes

Patients with cancer have a high risk of arterial cerebrovascular ischemia, twice as high as the general population [72, 73]. The risk is highest before primary tumor treatment, in gastrointestinal adenocarcinomas, in brain tumors, in patients who have had neck irradiation to treat head/neck neoplasms, and in advanced stages [74].

In a large population-based study, brain and GI tract tumors (colorectal, pancreas, and liver) had the highest mortality rates; stroke clustered in patients treated for brain

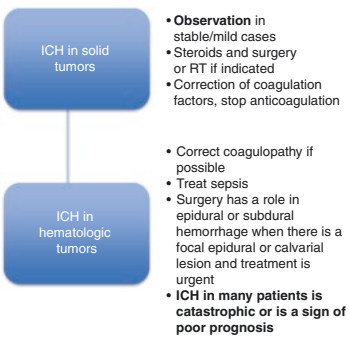

Fig. 16.11 Treatment alternatives in intracranial hemorrhage

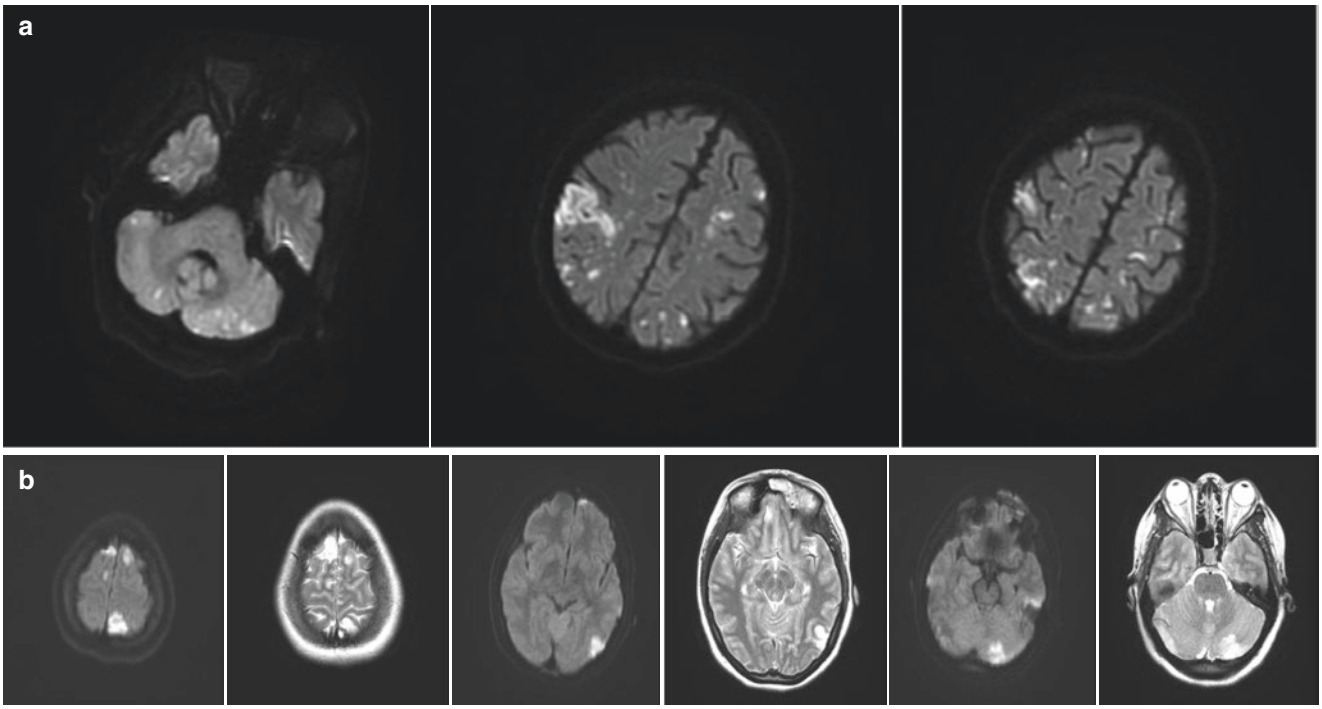

Fig. 16.12 (**a**) Axial, diffusion-weighted imaging (DWI) sequence. Multiple, bilateral embolic infarcts visible in cerebellum and supratentorial areas of a 65-year-old woman with lung adenocarcinoma. Transesophageal echocardiogram showed aortic valve leaflet with thrombus in the right atrium. (**b**) Multifocal cerebral and cerebellar diffusion restriction signals in DWI/T2 sequences. Cortical infarcts in multiple vessel distributions in a 26-year-old patient with sarcoma. MRA/MRV/2D echocardiograms were normal. These cortical strokes are due to meningeal pial penetrating arteries infiltrated by carcinomatosis meningitis or bacteria. In this case, bacterial meningitis. Source: an intravenous pain pump

tumors and lymphomas if younger than 40 years and in prostate, breast, and colon if older than 40 years of age [73]. The classical, conventional stroke risk factors so prevalent in the US population compound the risk even more: age; hypertension; atrial fibrillation; obesity; diabetes; and hypercholesterolemia. Other powerful stroke triggers in cancer patients, ranked from more to less common [5, 74], include (1) hypercoagulability and disseminated intravascular coagulation (DIC); (2) nonbacterial thrombotic endocarditis (NBTE) (Fig. 16.12a); (3) septic emboli (bacterial or fungal) (Fig. 16.12b); (4) tumor emboli; and (5) accelerated atherosclerosis after radiation therapy (Fig. 16.13).

Diagnosis

Most cancer patients in the ED present with three well-defined stroke syndromes [74, 75]. Those with *focal neurological deficits* (e.g., aphasia, hemiparesis, hemi-inattention, or homonymous temporal hemianopsia) are the most straightforward. Postictal deficit (Todd paralysis) should be included in the differential diagnosis, as it is a notorious stroke mimic among cancer patients. *Delirium* without focal signs is a more significant diagnostic challenge. Encephalopathic patients may present without lateral signs (focal deficits). ED providers *must* include ischemic stroke in the differential diagnosis of patients with delirium and no other apparent neurological deficits. Multiple, bilateral embolic infarcts in the carotid and vertebrobasilar territories are common in this group [74, 76]. Finally, patients may present with *both focal deficits and delirium*.

Assessment, Treatment, and Prognosis

The diagnostic sequence is similar to the diagnosis of stroke in the general population. An initial CT head without contrast screens for hemorrhage. The best tool to confirm the diagnosis is brain MR with diffusion-weighted imaging (DWI). Apparent diffusion coefficient (ADC) values may indicate areas of ischemic penumbra, and if there is no description of ADC changes in the radiology report, the emergency physician should ask about them. Fluid-attenuated inversion recovery (FLAIR) will help determine the approximate age of the ischemic lesion, and T1 without gadolinium and gradient echo (GRE) will assist in the diagnosis of hemorrhagic transformation from reperfusion injury, a spontaneous event in ischemic strokes or after thromboly-

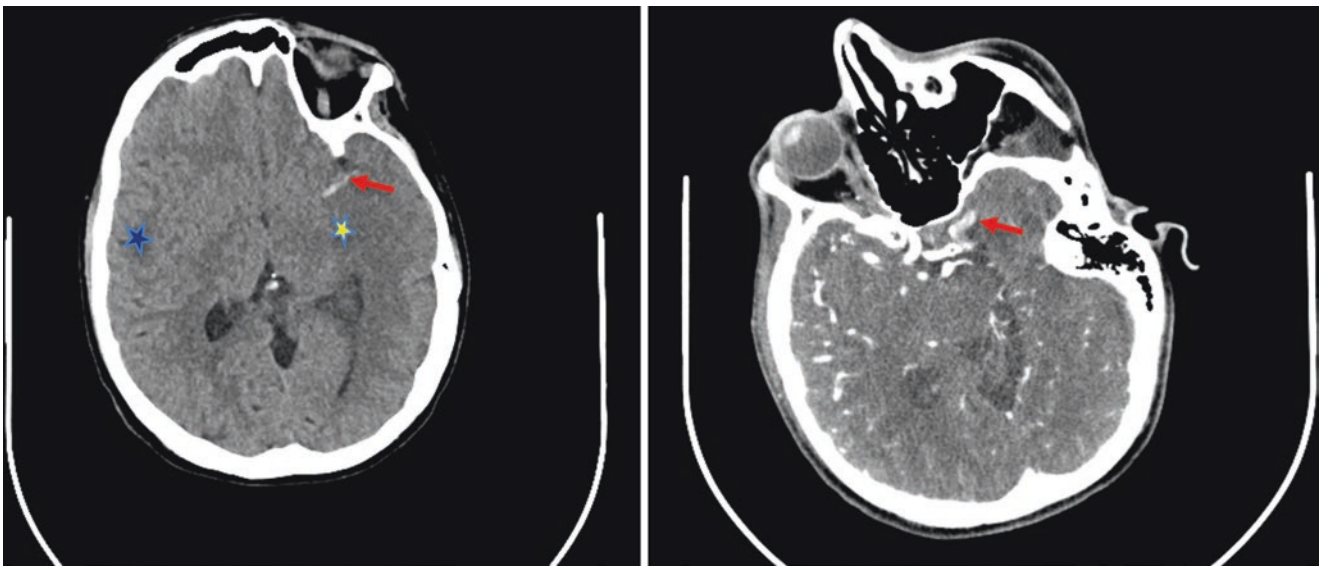

Fig. 16.13 47-year-old woman with history of left oral cancer, treated with radiation and chemotherapy 7 years before. She came to the ED with acute onset aphasia, right hemiparesis, and fall. National Institutes of Health (NIH) Stroke Scale score: 20. CT of head (*left panel*, *arrow*): classic hyperdense middle cerebral artery (MCA) sign from acute thromboembolic occlusion. Also: loss of left insular ribbon from cytotoxic edema, suggesting onset longer than 6 h (*yellow star, compared to blue star on the right*). *Right panel:* CT angiogram. Thrombus in the left internal carotid artery

sis. Finally, an MR angiogram of head and neck and MR venogram can assess for extra- or intracranial stenosis, vasculitis, and venous or sinus thrombosis.

The treatment of acute stroke is conditional to the status of underlying cancer or intercurrent complications derived from the tumor or its treatment. It is obviously more straightforward to treat patients in remission and not on active therapy than patients with complications of chemotherapy, sepsis, or active DIC.

In principle, all patients should have control of hypertension, diabetes, and hypercholesterolemia. If no contraindications exist, aspirin 325 mg daily for secondary prevention and oral anticoagulation for patients with atrial fibrillation are appropriate. Aspirin 100 mg daily for primary prevention of cardiovascular or cerebrovascular events in cancer patients has no evidence for widespread use yet and requires a thoughtful benefit-harm discussion based on patient preference [77]. Patients within 4.5 h of stroke onset are candidates for iv thrombolytics, as long as there is no absolute contraindication [78, 79]. A brain tumor is not in itself a contraindication, but a recent hemorrhagic metastasis poses additional risk, and most patients arrive past the therapeutic window, are too unstable, or have contraindications to thrombolytic therapy. Only 1.6% of patients with cancer and acute stroke receive iv thrombolytics or endovascular therapy [78].

The prognosis of acute ischemic stroke in patients with cancer is generally poor [80]. In patients after thrombolytics, the 3-month mortality is about 50%, and among survivors, 50% had a poor functional outcome. Patients with solid tumors and metastases have worse outcomes than patients with hematologic malignancies. In those undergoing antineoplastic therapy, a stroke resulting in worse functional outcome means poor performance. This consequence has relevance for goals of care, quality of life, and eligibility for clinical trials, among other issues.

Cerebral Venous Sinus Thrombosis

Frequency

Venous sinus thrombosis occurs in 9% of adults with hematologic malignancies or solid tumors. It affects more women than men and tends to happen within the first year of cancer diagnosis [81].

Presentation

Headache, confusion, and seizures are common presentations. As in other emergencies, the severity of symptoms varies from an incidental finding to coma. Younger patients tend to present with headache and papilledema (increased ICP), whereas older patients (>50 years) have more AMS [82].

Diagnosis

A venogram by CT or MRI is the most direct means of non-invasive diagnosis [83]. The regular MRI of the brain can point to the suspect area before the angiogram.

Treatment and Prognosis

If asymptomatic, we tend to treat with anticoagulation, with admittedly little evidence that this approach is better than observation. For symptomatic, stable patients, supportive measures are the first steps, followed by anticoagulation with subcutaneous low-molecular-weight heparin (LMWH). The optimal duration is unclear, but many patients receive treatment for 3 to 6 months, and some permanently, reflecting how little we know and the need for well-controlled studies. Thrombectomy and thrombolysis with the tissue plasminogen activator (tPA) are effective interventions in selected cases. We have no experience with these agents as most of our patients have contraindications, or their prognosis is poor. For stable and symptomatic patients, the prognosis for survival and neurologic function is good. For patients with an acute presentation with brain herniation and CSE, the outlook is poor with a high mortality rate. Predictably, the prognosis for survival or recovery in cancer patients is worse than in non-cancer patients [75].

Case Studies

Case Study 1: Pembrolizumab-Associated Myopathy

A 73-year-old man with renal cell carcinoma, bone, and lung metastases began treatment with pembrolizumab (ICI) every 21 days and axitinib (a tyrosine kinase inhibitor). After cycle 4, patient came to the ED with diffuse bilateral muscle tenderness and weakness, ascending to involve neck and bulbar muscles. On examination, he exhibited severe neck ptosis (antecollis), eye ptosis, dysarthria, and dysphagia (requiring a feeding tube). He had acceptable respiratory function, without need for supplemental oxygen. Before arrival, he had received IVIG and high-dose prednisolone at another institution with partial improvement.

Our initial clinical diagnosis was acute inflammatory myopathy. There is a clear association between ICI, myositis, and myasthenia gravis. His CK levels rose from 49 U/L on admission to 545 U/L on day 19 (72 h after admission) and 343 U/L on day 21. EMG was consistent with myositis in the cervical paraspinals and trapezii. A muscle biopsy was nondiagnostic twice and anti-titin and striatal antibodies were negative.

He was treated with plasma exchange and rituximab 375 mg/m2 BSA days 1 and 15, plus infliximab 5 mg/kg days 1 and 15. Steroids were tapered over 6 weeks. Mild neurological disability persisted, and although the patient is ambulatory, he still speaks in a low voice and has slurred speech and dysphagia for solids.

Case Study 2: Atezolizumab-Associated Meningoencephalitis [50]

A 53-year-old woman with metastatic squamous cell carcinoma of the cervix was referred to the ED by her gynecologic oncologist for evaluation of headache and AMS for 24 h. Thirteen days earlier she had received her first doses of atezolizumab and bevacizumab.

She was found to be delirious, with nuchal rigidity. Laboratory evaluation revealed a normal absolute neutrophil count (ANC), lymphopenia, and a white blood cell count of 3.4 10^9/L. Brain MRI suggested diffuse leptomeningeal enhancement along the cerebral sulci and cerebellar foliae (Fig. 16.14). *Supportive care was initiated in the ED. She was transferred to the ICU and treated with dexamethasone* (Fig. 16.15).

On day 6 after admission, her mental status deteriorated. A routine EEG showed a pattern of nonconvulsive status that responded readily to lorazepam (Fig. 16.16). *After this event, the patient steadily recovered, and corticosteroids were tapered after 21 days of therapy. She had no residual neurological disability and became fully independent.*

Case Study 3: CAR T-Cell Neurotoxicity

A 58-year-old man with diffuse large B-cell lymphoma was in relapse after multiple lines of treatment. He had received axicabtagene ciloleucel (YESCARTA®) on day 0 and on day 3, and he exhibited cytokine release syndrome (CRS) grade 2 with fever, fatigue, nausea, and malaise. He was managed accordingly, with symptomatic treatment and observation in the fast-track clinic as an outpatient. This mild CRS was resolved by day 8 when his family brought him to the ED for acute onset confusion. He was alternating between moments of combativeness with sleepiness, and this was a departure from his normal behavior.

On examination the emergency physician found that patient was disoriented, with no attention span, and mostly uncooperative. He could not speak in complete sentences, and could not write when his relative gave him a paper and pen to help him communicate. There was no evidence of concurrent CRS, and the ED physician diagnosed neurotoxicity grade 2 related to YESCARTA®. He was treated immediately with dexamethasone 10 mg iv q6h and admitted. He also began levetiracetam, a bolus of 20 mg/kg and maintenance dose of 1000 mg iv q12h. Besides sinus tachycardia, all vitals were normal, and laboratory values, including liver and

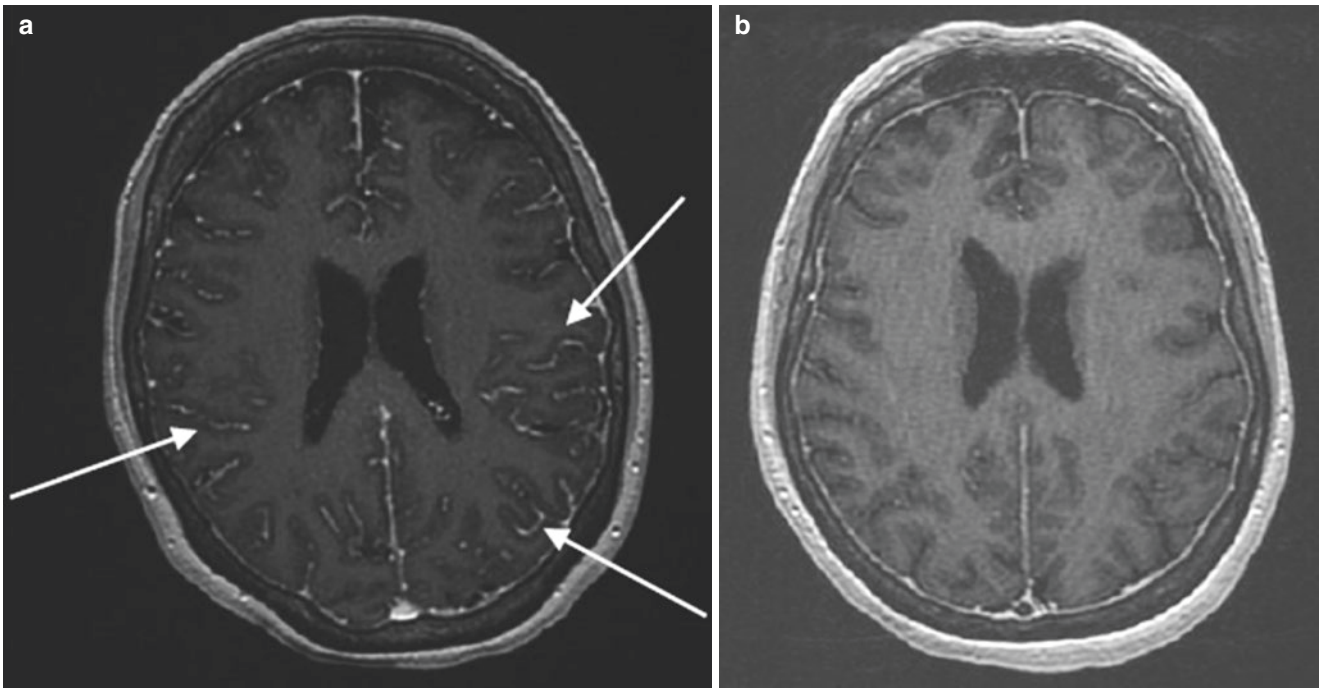

Fig. 16.14 *Case study 2*: (**a**) axial MR brain, T1 with contrast, leptomeningeal enhancement (*arrows*) in case study 2, on day 2 of symptom onset. (**b**) At day 8, after high-dose iv steroids

Dexamethasone 4mg/day ↑24 mg/day

Opens eyes, follows commands

Dexamethasone tapered over 21 days

CSF (units)	Day 0	Day 7	Day 15
WBC (10^9/L)	553 (H)	9 (H)	3
Protein (g/L)	>600 (H)	302.0 (H)	71.0 (H)
Beta 2 Microglobulin (mcg/mL)		10.0 (H) 0.7 - 1.8 mg/L	
MBP (ng/mL)		21.30 (H) 5.50 ng/mL	
Albumin (mg/dL)		119.0 (H)	22.7
Cytology	Numerous acute inflammatory cells	-	-

Fig. 16.15 *Case study 2*: Treatment course, with serial cerebrospinal fluid (CSF) findings revealing high CSF white blood cells, protein, beta-2-microglobulin, and basic myelin protein levels

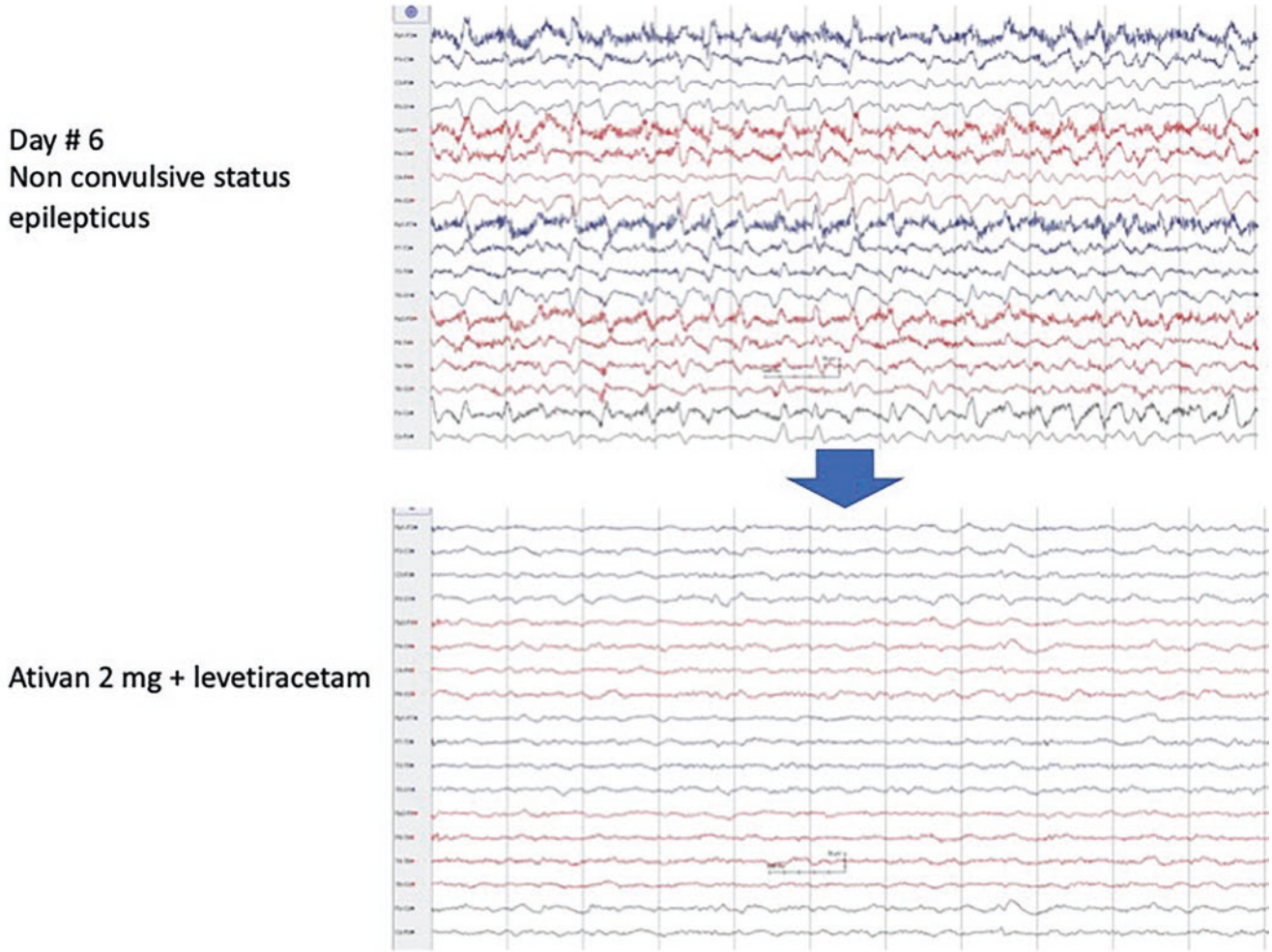

Fig. 16.16 *Case study 2:* acute altered mental status on day 6, with EEG diagnostic of nonconvulsive status before (*upper panel*) and after treatment with antiepileptic drugs (*lower panel*)

renal parameters, were normal. Urine analysis and chest x-ray were unremarkable.

The patient went to the regular floor where dexamethasone continued for 4 more days (day 12). He improved steadily within 72 h and was at baseline by day 14. His treating team stopped dexamethasone and the patient was discharged.

Comment: In the trials leading to the FDA approval of YESCARTA®, 85% of patients had neurotoxicity, 31% of them grade 3 or higher. Most cases (98%) happened within 8 weeks of the infusion day (day 0), with a median onset at 4 days (range: 1–43 days). Our patient began neurological symptoms on day 8. The median duration of neurotoxicity is 15–17 days, with rare cases having encephalopathy for almost 6 months. For grade 2 toxicity and no concurrent CRS, dexamethasone, AED, and hemodynamic monitoring in a regular floor are appropriate.

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Pituitary Apoplexy

17

Daria Krivosheya and Ian E. McCutcheon

Case Study

A 78-year-old woman had an intense headache and nausea, both of sudden onset, and consulted her family physician. Noting hypertension to 189/96, he treated her with clonidine and morphine. She presented with unrelieved headache to her local emergency department (ED) the following day, where an MRI showed a sellar and suprasellar mass, the heterogeneity of which suggested hemorrhage within a pituitary macroadenoma (Fig. 17.1). *This hemorrhagic component was not, however, recognized at that time. The tumor did not reach the optic chiasm. Cerebral atrophy and chronic ischemic demyelination were also seen, consistent with her age. No endocrine workup was undertaken. Her analgesic was changed to hydromorphone 2 mg by mouth, four times daily. Nonetheless, her headache persisted, and she became forgetful and was excessively sleepy. Her family sought a second opinion 5 days after the ED visit. At that time she was somnolent but had clear mental status when aroused. She said she felt "tipsy" much of the time. She showed no cranial neuropathies, and no visual field deficit. She had tenderness and swelling on the dorsolateral aspect of her right foot but had no recollection of the fall that had caused this local contusion. Her endocrinological history included diabetes mellitus controlled by metformin and Graves' disease with hypothyroidism after 131I treatment of that condition. She also took methotrexate for rheumatoid arthritis.*

On laboratory workup, the following values were obtained: sodium, 119 mEq/L; serum osmolality, 253 mOsm/kg of water; urine osmolality, 217 mOsm/kg of water; magnesium, 1.4 mg/dL; and glucose, 148 mg/dL. Hormonal assessment showed the following: cortisol, 3.9 mcg/dL (normal, 4.4–12.4); ACTH, <5 pg/mL; prolactin, 11 ng/mL; luteinizing hormone, 1.6 mIU/mL; follicle-stimulating hormone, 12.8 mIU/mL; free T4, 1.20 ng/dL; and thyroid-stimulating hormone, 0.49 μIU/mL. She also had a possible urinary tract infection with 19 WBC/hpf and 7 hyaline casts/hpf; cultures of urine and blood were negative.

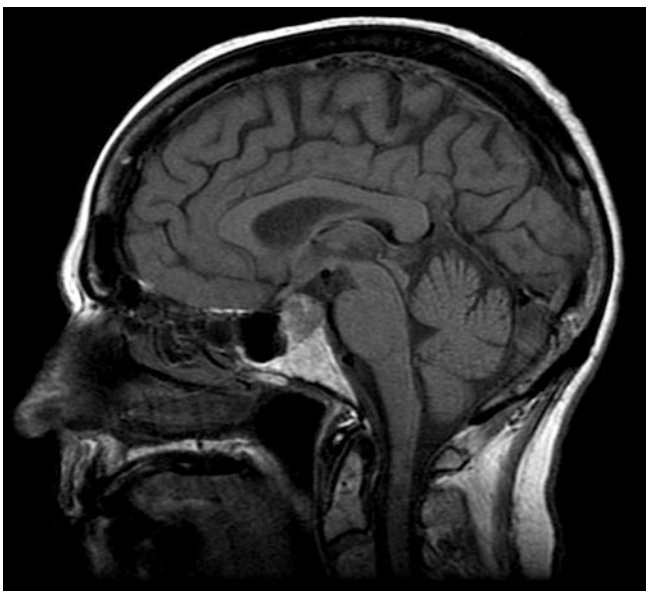

Fig. 17.1 Pituitary macroadenoma with heterogeneity (areas of both hyperintensity and hypointensity) on pre-contrast MRI, sagittal view

She was admitted to hospital for the following diagnoses: clinically nonfunctional pituitary macroadenoma with pituitary apoplexy; syndrome of inappropriate ADH secretion causing severe hyponatremia; diabetes mellitus, poorly controlled; hypertension; central hypogonadism; cellulitis of the right foot; and headache. Her treatment included transsphenoidal removal of pituitary tumor and associated hemorrhage; fluid restriction; glyburide; adjustment of clonidine; Levaquin x 5 days; discontinuation of hydromorphone; and initiation of hydrocodone/acetaminophen.

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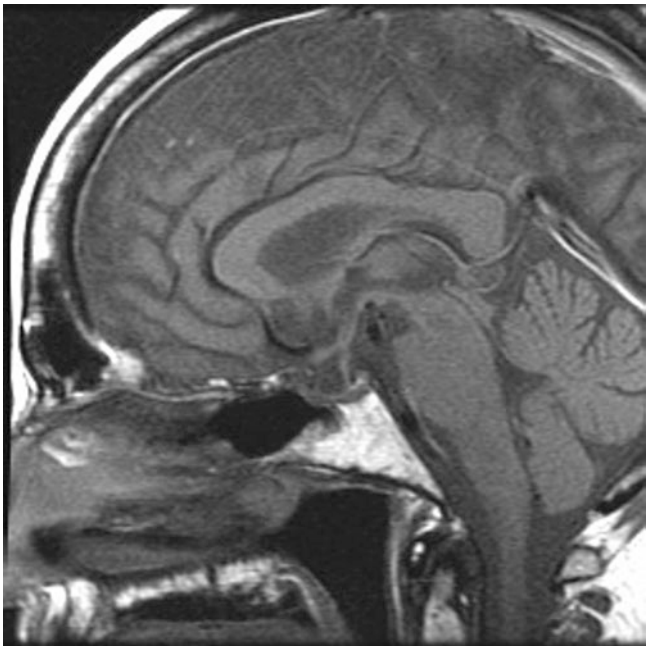

Fig. 17.2 Sella (MRI, pre-contrast, sagittal view) showing preservation of pituitary gland after complete removal of pituitary macroadenoma and associated hemorrhage

Transsphenoidal removal of the pituitary tumor was done 10 days after her admission (Fig. 17.2). *The tumor was removed in gross total fashion, and in the 6 years since, it has not recurred. Although some cases of pituitary apoplexy demand more immediate surgical intervention, in this patient the tumor was not producing visual loss, and her obtundation was provoked by the unhappy combination of profound hyponatremia and over-medication with a powerful narcotic analgesic. The presence of an unrelated cellulitis required treatment prior to surgery, and time was needed for correction of her hyponatremia, hyperglycemia, and hypocortisolemia in order to reduce surgical risk. Thus, a delayed surgical approach was chosen. Her headaches diminished as serum sodium returned to normal levels and disappeared once the tumor had been removed.*

This case offers several important lessons in the management of pituitary apoplexy. It is essential to recognize the MRI signature of hemorrhage in a pituitary adenoma, as the presence of apoplexy raises significantly both the urgency of treating it, and the concomitant risk of pituitary hypofunction. When any pituitary tumor is found, measuring hormone levels and serum electrolytes is essential. Severe headaches caused by a pituitary tumor are best treated by eliminating the tumor, and opioids should not be used at such a high dose in an elderly patient, in whom adverse effects are achieved at lower dose levels than in younger people. It is important to treat any potential inciting causes of pituitary apoplexy (e.g., hypertension or coagulopathy) present when a diagnosis of pituitary apoplexy is made, but treatment is only sufficient when the tumor itself is also treated. Hyponatremia is an important consequence of pituitary apoplexy and should be treated before surgery is undertaken. The same is true for low levels of serum cortisol, which must be corrected with steroid supplementation prior to an operation. Finally, even a complex medical situation in a sick patient with pituitary apoplexy can be managed effectively and safely if a deliberate, thoughtful, careful approach is used, so that surgery can be done effectively and safely.

Definition

Pituitary tumor apoplexy is a clinical syndrome, the hallmarks of which include headache, ophthalmoplegia, and altered level of consciousness. Hemorrhagic infarction of a pituitary tumor leading to rapid expansion of the contents of the sellar region and subsequent acute pituitary gland dysfunction is the underlying basis for this syndrome. The first case of pituitary apoplexy was described by Pierce Bailey in 1898 [1]. However, the term "pituitary apoplexy" was first introduced by Brougham et al. in 1950 in a case report describing five cases of hemorrhagic infarction of pituitary adenomas [2]. The word apoplexy derives from Greek (*apoplēssein* = to strike down, disable) and means in modern parlance the sudden onset of a neurological deficit, as when a stroke, in a setting of bleeding, results in abrupt loss of function. While nowadays we refer to such bleeding as hemorrhagic stroke, the term apoplexy has remained in use to describe hemorrhage in the pituitary region. Such hemorrhage in most cases occurs when a pituitary tumor is present, and as such, some authors argue that this condition would be more accurately described as pituitary tumor apoplexy [3].

Hemorrhage into a pituitary adenoma with resulting clinical symptoms is also called classical pituitary apoplexy. Spontaneous silent hemorrhage can occur in up to 25% of pituitary adenomas, and when discovered incidentally during routine imaging or histopathologic examinations, it is referred to as subclinical pituitary apoplexy [4, 5]. Pituitary apoplexy has to be distinguished from hemorrhage into a Rathke's cleft cyst, a very rare event whose clinical presentation is identical to pituitary tumor apoplexy syndrome [6–8]. Furthermore, infarction of the pituitary gland during a prolonged or severe period of hypotension is well described in pregnancy and post-partum and is referred to as Sheehan's syndrome [8–10]. The following discussion is dedicated to the diagnosis, management, and outcomes of classical pituitary apoplexy caused by bleeding in a pituitary adenoma.

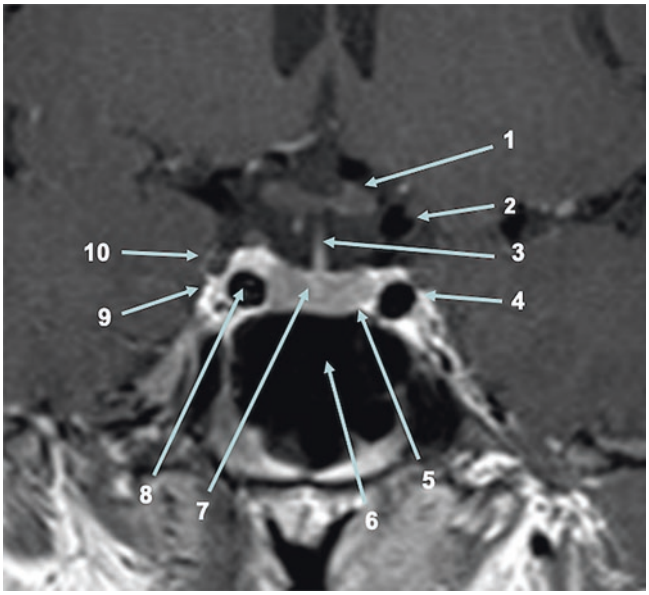

Fig. 17.3 Post-contrast MRI (coronal, T1-weighted image) showing the anatomical structures in the sella and parasellar region. (1) Optic nerve; (2) suprasellar internal carotid artery; (3) pituitary stalk; (4) lateral wall of cavernous sinus; (5) medial wall of cavernous sinus; (6) sphenoid sinus; (7) pituitary gland; (8) intracavernous carotid artery; (9) abducens nerve (nerve VI); and (10) oculomotor nerve (III nerve)

Anatomy and Physiology Review

To understand the clinical presentation of pituitary apoplexy, it is essential to review the contents of the sellar region and how the apoplectic event disturbs them (Fig. 17.3). Its clinical symptoms can be associated with the sudden onset of one (or more) of four events: presence of intracranial blood; acute onset of pituitary gland dysfunction; loss of vision; and cranial nerve dysfunction, usually manifesting as diplopia.

The presence of acute intracranial blood is a major source of headache. While in most cases of pituitary apoplexy the blood is contained within the tumor, there can be subarachnoid extension of the hemorrhage. Thus, ancillary tests are necessary to rule out a vascular cause of subarachnoid blood such as an aneurysm or a vascular malformation.

The pituitary gland is located within the sella turcica of the sphenoid bone. The gland comprises two parts: an anterior lobe that produces six hormones, including growth hormone (GH), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and prolactin, and a posterior lobe, the site of delivery and release of oxytocin and vasopressin produced in the hypothalamus. Acute hemorrhage into the anterior pituitary can result in sudden cessation of secretion of one or more of these hormones. Of the above hormones, acute deficiency of ACTH is of upmost importance as it results in a blunted cortisol response to stress, which if severe enough can be associated with profound hypotension and hyponatremia. Although dysfunction of the posterior pituitary causes alteration of vasopressin secretion leading to central diabetes insipidus and associated hypernatremia, it is rarely observed clinically. Since almost all pituitary adenomas arise in the anterior lobe, they mainly affect the function of that part of the gland. Prolactin, on the other hand, is secreted by the anterior lobe and rises in response to pituitary stalk compression, or when the adenoma itself secretes prolactin. While acute alterations of serum prolactin level do not affect the clinical picture, initial and subsequent prolactin levels have diagnostic significance and thus should be measured.

The two cavernous sinuses are located on either side of the pituitary gland. These venous structures enclose the internal carotid arteries as well as cranial nerves III, IV, and VI. The latter control eye movements, and dysfunction of any of these nerves results in abnormal eye movements on directed gaze with the subjective report of diplopia. Profound compromise of cranial nerve III can also cause eyelid closure. Finally, the optic nerves and chiasm are located in the suprasellar region, and with sufficiently large lesions, compromise of visual acuity and/or fields may occur.

Clinical Presentation

Familiarity with the anatomical structures of the sellar region allows one to understand the symptoms that patients may experience after hemorrhage in that area. The spectrum of presentation of pituitary apoplexy correlates with the size of the hemorrhage and degree of injury to the surrounding structures. While small hemorrhages may be detected radiographically in otherwise asymptomatic patients, a condition referred to as subclinical apoplexy, large hemorrhages can present with an acute alteration of consciousness, cardiovascular collapse, and obtundation, and they can be life-threatening. Between these two extremes lies a spectrum or constellation of clinical signs that can include headache, changes in vision including diplopia, and various degree of pituitary hypofunction (Fig. 17.4). A given presentation may include one or many of the above signs and symptoms. The most common presenting clinical symptoms are summarized in Table 17.1. The typical ranges of demographics and predisposing or associated factors are shown in Table 17.2 [11].

Headache

Headache is the most common symptom observed in pituitary apoplexy, occurring in 95% of patients [9, 12]. The etiology of headache is likely multifactorial. The rapid increase in pressure within the intrasellar compartment as a result of the hemorrhage causes stretching of the dura lin-

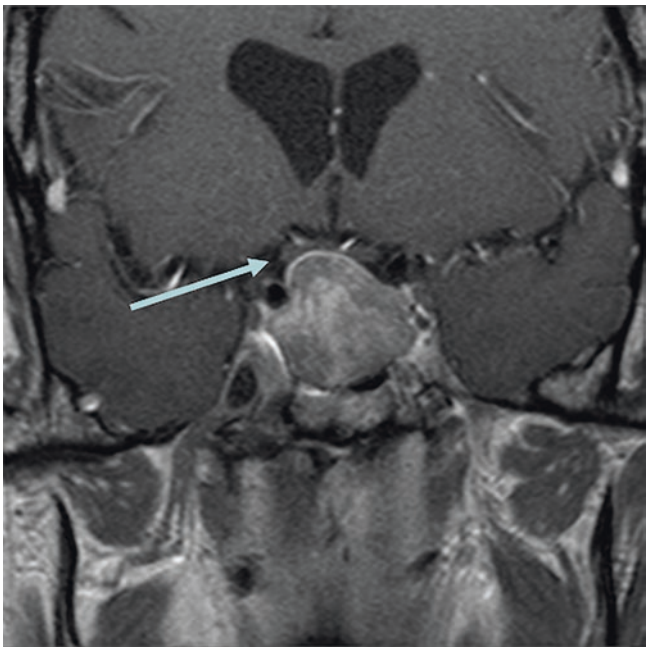

Fig. 17.4 Pituitary macroadenoma with intratumoral hemorrhage (= pituitary apoplexy). This tumor has expanded into the suprasellar space and compresses the optic nerve and chiasm, with resulting onset of severe headache and a temporal visual field deficit. The patient also has profound hypopituitarism. Surgical removal of this hormonally nonfunctional tumor is indicated

Table 17.1 Common presenting clinical features of pituitary apoplexy

Clinical symptom
Headache
Nausea and vomiting
Decreased visual acuity
Visual field deficit
Diplopia
Cranial nerve palsy (III, IV, or VI)
Altered mental status
Seizure
Collapse/shock
Coma

ing the sella and produces the resulting headache. Leakage of blood from the hemorrhagic tumor into the subarachnoid space can contribute as well. Vomiting is observed in 70% of patients presenting with a headache and can stem from increased intracranial pressure or from pituitary hypofunction [14]. Headache associated with pituitary apoplexy is most commonly "thunderclap" in nature and tends to respond to resection of the underlying hemorrhagic tumor. When a conservative (non-operative) strategy is chosen, drugs that inhibit platelet aggregation should be avoided and opioid usage limited to prevent clouding of the patient's sensorium [13].

Table 17.2 Clinical correlates of pituitary apoplexy [11]

Gender (male/female) (no.)	48/52
Demographics	(%)
Patients with apoplexy as first presentation of pituitary disease	73
Patients with apoplexy and prior known pituitary disease	27
Predisposing/associated factors[a]	
Prior diagnosis of hypertension	33
Pregnant or post-partum	13
Diabetes mellitus	8
Antiplatelet or anticoagulant medication	6
Dopamine agonist	4
Radiotherapy	4
None	46
Secretory status of associated adenoma	
Nonfunctional or gonadotroph adenoma	90
Prolactin-secreting adenoma	10

[a]Some patients had more than one predisposing factor

Visual Disturbance

Visual symptoms observed in cases of pituitary apoplexy include either optic nerve dysfunction or diplopia. The optic apparatus, which includes optic nerves, optic chiasm, and optic tracts, is located in the suprasellar compartment and can be subject to direct pressure from the expanding hematoma. Such pressure most commonly provokes bitemporal visual field restriction due to pressure against the undersurface of the chiasm. Direct pressure on one or both nerves or tracts could also result in changes in visual acuity, culminating in a central or junctional scotoma. The latter results in the superior temporal defect in one eye and decreased central vision in the other eye as a result of compression of anterior chiasm, the site of anteriorly looping fibers from the contralateral nasal retina (Fig. 17.5).

Diplopia is another very sensitive presenting symptom of pituitary apoplexy. Cranial nerves that control eye movements, namely III, IV, and VI, run within the cavernous sinus on either side of the sella and are highly susceptible to compression (see Fig. 17.3). Cranial nerve III dysfunction is observed most frequently and can present as ptosis, a dilated pupil and an eye that looks down and out with inability to adduct. Cranial nerve VI innervates the lateral rectus muscle of the eye and controls eye abduction; thus, dysfunction results in inability of the eye to look outward.

Pituitary Dysfunction

Up to 80% of patients with pituitary apoplexy present with pituitary dysfunction [12, 15–17]. While any of the pituitary hormones can be affected, acute decrease in ACTH secretion with subsequent hypocortisolism is the most clinically sig-

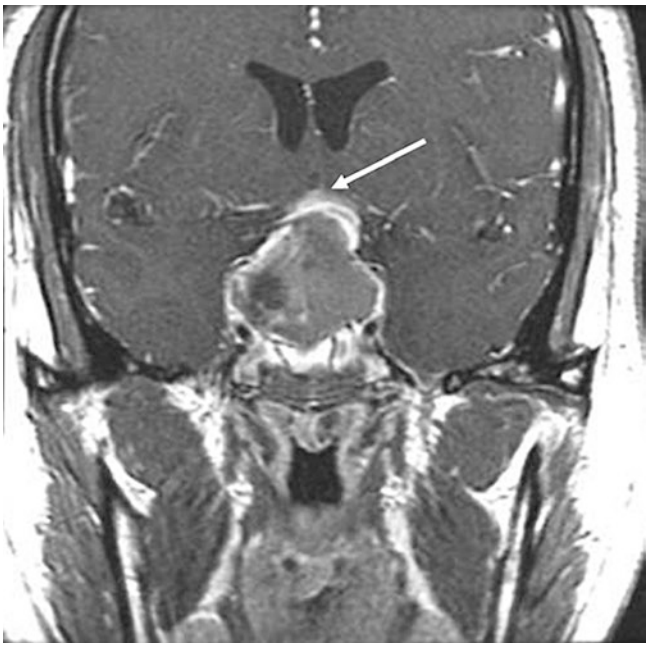

Fig. 17.5 Nonfunctional pituitary macroadenoma expanded by hemorrhage and causing a bitemporal visual field deficit. The arrow points to the area of impaction on the optic chiasm. Note the fuzzy, ill-defined hyperintensity present; this is subarachnoid blood that leaked through a disrupted diaphragm sellae. This patient's vision returned to normal after transsphenoidal removal of the tumor and associated hemorrhage

nificant endocrinopathy. Acute adrenal insufficiency can precipitate hypotension (shock) but may also present with hyponatremia, hypoglycemia, nausea, vomiting, obtundation, and coma [18].

Serum prolactin levels at presentation may reflect the degree of pituitary compression and thus give an indirect, albeit imperfect, indication of intrasellar pressure. Low prolactin levels indicate a high degree of pituitary compression and less chance of recovery from hormone impairment after a decompressive procedure [19].

While other pituitary hormones may be affected as a result of pituitary hemorrhage, the reported incidence of these abnormalities varies greatly. Although ACTH dysfunction is most clinically important, it is crucial to identify dysfunction in other hormonal axes as well. GH deficit is seen in 88% of cases, ACTH dysfunction in 66%, TSH abnormality in 42%, and loss of FSH and LH in 85% of cases of pituitary apoplexy [20, 21].

On rare occasions apoplexy causing global infarction of a functional adenoma can cause spontaneous remission of the patient's clinical symptoms of hormonal excess, as well as correction of the relevant hormone levels. This phenomenon has been reported in patients with moderately sized adenomas causing acromegaly or Cushing's disease [22].

Incidence and Predisposing Factors

The true incidence of pituitary apoplexy is difficult to estimate, as many cases are asymptomatic. The reported incidence for symptomatic hemorrhage ranges from 2% to 7% of all pituitary adenomas [12, 15, 16]. In 80% of patients with pituitary apoplexy, the initial diagnosis of hemorrhage is made at the time the tumor is first discovered [23]. There is a slight male predominance for hemorrhage into a pituitary tumor, and most patients present in their fifth or sixth decade [17, 24, 25].

It has been estimated that pituitary adenomas are five times more likely to bleed compared to other tumors [26]. Several characteristics of pituitary adenoma have been identified that put patients at this increased risk of apoplexy. Gender, age, and specific hormonal subtypes carry no increased risk of apoplexy compared to matched controls [21]. An increased risk of hemorrhage is, however, observed in patients with a history of hypertension [12, 17]; usage of anticoagulants or antithrombotic medications [27, 28], estrogen therapy [29], or dopamine agonists [16, 30]; or dynamic testing of pituitary function (see Fig. 17.5) [31, 32]. Rarely, a patient with a pituitary adenoma sustains a head injury that provokes apoplexy [33]. One factor more consistently associated with a higher incidence of apoplexy is tumor size; macroadenomas are much more likely to present with intratumoral hemorrhage than are microadenomas [15, 34–37]. Furthermore, some series have shown that in many cases there is an associated area of infarction within the tumor; thus it is not clear whether the initial event is infarction or hemorrhage [38, 39].

Several hypotheses have been put forward to explain what causes ischemia and hemorrhage in pituitary adenomas. One theory postulates that as a tumor enlarges, it compresses its own blood supply, eventually leading to ischemia and hemorrhage. On the other hand, tumor enlargement may be associated with the tumor's outstripping its own blood supply, thus leading to ischemic necrosis. The higher incidence of hemorrhage into an ischemic or necrotic area within a pituitary adenoma may relate to the unique vascular supply of these tumors [34].

The unique blood supply to the pituitary gland has been implicated in predisposing these tumors to hemorrhage. The pituitary gland is supplied by the hypophyseal portal system. The blood supply to the anterior pituitary comes from the superior hypophyseal arteries, branches of the internal carotid artery that travel along the pituitary stalk and form a rich vascular portal system. The posterior pituitary receives its blood supply from the inferior hypophyseal arteries, which are terminal branches of the meningohypophyseal trunk of the internal carotid artery. There are many anasto-

moses between the hypophyseal network on and in the pituitary gland and the portal vascular on the pituitary stalk [40]. Pituitary adenomas receive their blood supply from the portal system, as well as directly from the hypophyseal vessels. This exposes the pituitary adenoma to systemic blood pressures. The presence of hypertension with the rich and complex network of the portal system increases the risk of bleeding by fivefold compared to other tumors [13].

Inherent tumor characteristics have also been implicated in predisposing pituitary adenomas to ischemia and apoplexy [41]. Pituitary adenomas are metabolically active tumors that require a continuous supply of glucose and demonstrate a high glucose uptake in 18F-fluorodeoxyglucose-PET studies [42]. Interruption of glucose supply results in rapid adenoma cell death and may lead to infarction [41]. Furthermore, pituitary adenomas have a low level of secretion of such angiogenic factors as vascular endothelial growth factor (VEGF) [43]; thus it is not surprising that they have a reduced vessel density on histological examination which clinically translates into decreased contrast uptake on imaging studies [44]. Finally, perfusion studies have demonstrated very low blood flow in pituitary adenomas [45], likely as a consequence of the high intratumoral pressure that is typical for these tumors [46], factors that predispose pituitary adenomas to a higher risk of developing ischemia. In summary, the combination of the microvascular architecture of pituitary adenomas with the resultant low blood flow and the inherently high metabolic demand of adenoma cells make these tumors very susceptible to ischemic injury during times of systemic blood pressure fluctuation and thus to development of intratumoral pituitary hemorrhage and clinical apoplexy.

Pituitary Apoplexy Workup

Differential Diagnosis

In a patient presenting with a severe headache, a number of other conditions should be considered and ruled out besides pituitary apoplexy. The differential diagnosis includes subarachnoid hemorrhage secondary to a ruptured aneurysm, meningitis, and hydrocephalus, among others. When visual loss and ophthalmoplegia point to pathology in the sellar region, cavernous sinus thrombosis, brain abscess, or a growing cerebral aneurysm should be considered. Other clinical conditions to be considered as part of the differential diagnosis for pituitary apoplexy include temporal arteritis, ophthalmoplegic migraine, hypertensive encephalopathy, basilar artery occlusion, and brainstem stroke or hemorrhage [21, 34].

Diagnostic Imaging

Visualization of the hemorrhage within the sellar region is necessary to make the definitive diagnosis of pituitary apoplexy. Computed tomography (CT) of the brain is a good initial study for detecting acute blood in the sellar region (Fig. 17.6) [47]. A hyperdense lesion in the sellar region on a non-contrast CT scan is highly suggestive of hemorrhage within the first 3 days after the event. Although this modality of imaging is sensitive for hemorrhage, it is not necessarily specific. As intracranial aneurysms and calcifications associated with the craniopharyngioma are also hyperdense on CT scans, it may be difficult to make a definitive diagnosis [35]. To characterize the lesion as well as the underlying pathology, magnetic resonance imaging (MRI) should be obtained [48].

The MRI T2-weighted gradient echo sequence is most sensitive for blood products and may detect even small hemorrhages. It is not, however, accurate at estimating the size or age of the hemorrhage. By surveying the corresponding T1- and T2-weighted sequences, it is possible to determine the age of the hemorrhage. The changes in signal intensity of the hemorrhage over time on T1- and T2-weighted MRI scans are summarized in Table 17.3. Furthermore, MRI allows better anatomical visualization of the pituitary gland and may help delineate the underlying tumor, as well as define the relationship of the tumor and the hemorrhage to the optic apparatus. It can also identify extension into either cavernous sinus and rule in or rule out an aneurysm [48–50].

Laboratory Investigations

Fluid and electrolyte disturbances are frequently observed in patients with pituitary apoplexy. Hemorrhage into the pituitary adenoma may affect the function of the pituitary gland itself. In fact, reduced ACTH secretion and resulting hypocortisolemia are observed in 80% of cases [12, 17, 51]. Acute adrenal insufficiency may lead to hyponatremia and, in severe cases, to cardiovascular collapse. Therefore, determination of serum electrolyte levels and fluid balance status is critical to avoid missing adrenal crisis in patients with pituitary apoplexy. Symptoms of acute adrenal insufficiency include vomiting, abdominal pain, myalgia, joint pains, and severe hypotension, leading to hypovolemic shock [18].

Other pituitary hormones can also be affected. TSH deficiency is noted in 50% of cases, and if pre-existing, it may lead to increased morbidity and mortality of pituitary apoplexy in the context of concurrent ACTH deficiency. Disturbance of the gonadotropin axis is observed in 75% of cases [12, 17, 51]. Prolactin levels should be measured, as

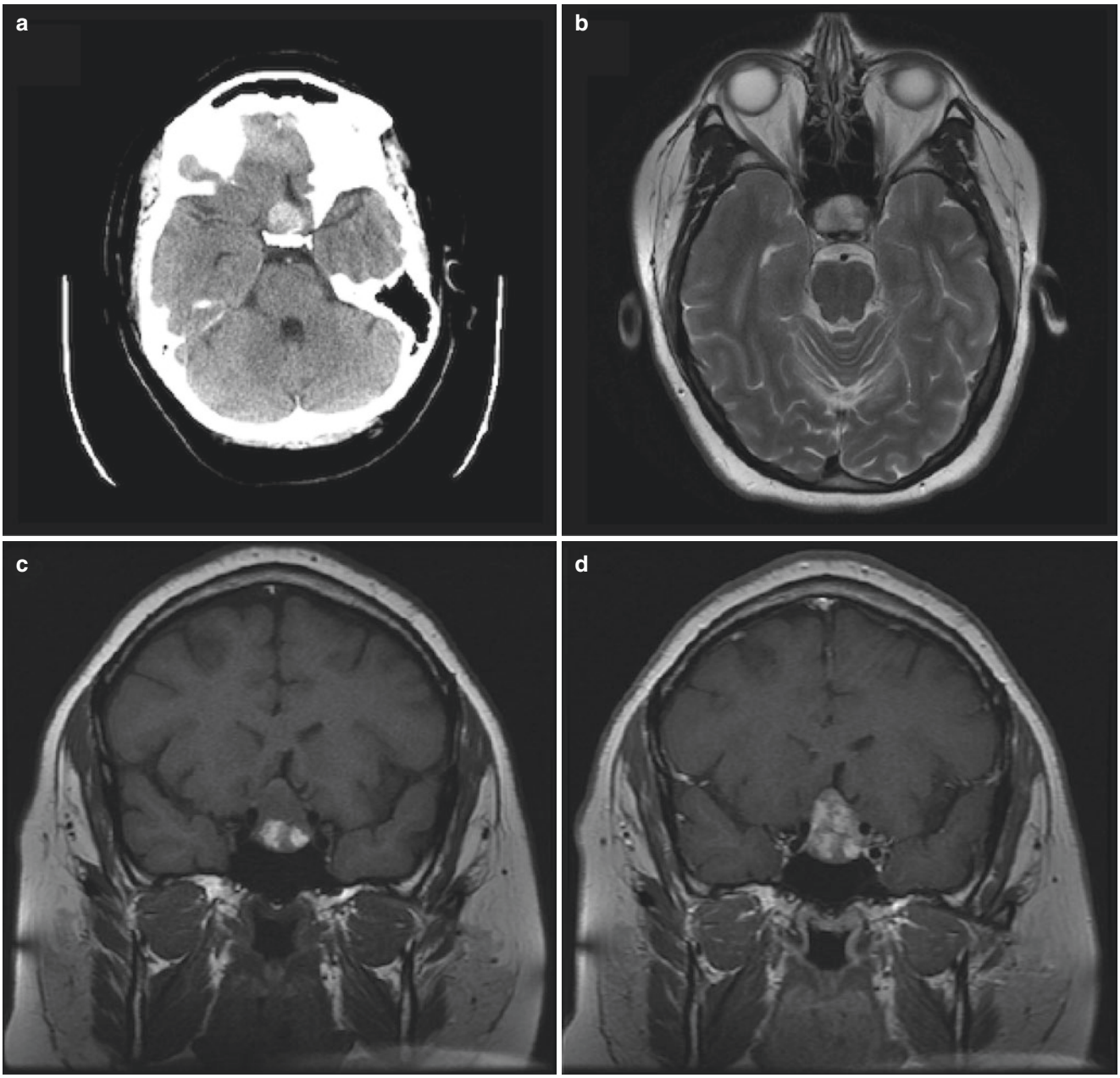

Fig. 17.6 Representative images for a patient with pituitary apoplexy. Non-contrast CT axial image (**a**) demonstrates a hyperdense lesion in the sellar region consistent with recent hemorrhage. The T2-weighted axial MRI image (**b**) demonstrates an expansile hyperintense lesion in the sellar region. The T1-weighted coronal slices through the sellar region (**c**, **d**) demonstrate a 2.5 cm lesion with an inferior hyperintense component consistent with subacute blood (**c**). The superior component of the tumor heterogeneously enhances with contrast administration, giving an appearance consistent with an underlying pituitary adenoma (**d**)

Table 17.3 Typical appearance of blood on T1- and T2-weighted MRI images

Stage of hemorrhage	Time	T1	T2
Hyperacute	<24 hours	Isointense	Hyperintense
Acute	1–3 days	Isointense	Hypointense
Early subacute	3–7 days	Hyperintense	Hypointense
Late subacute	7–14 days	Hyperintense	Hyperintense
Chronic	>14 days	Hypointense	Hypointense

lower levels of this hormone are predictive of the degree of pituitary compromise and of a higher likelihood of need for pituitary hormone replacement in the future [19].

Alteration of anterior pituitary function is often observed in cases of pituitary apoplexy. In contrast, function of the posterior pituitary gland is rarely affected. While transient hyponatremia in the acute period is frequently attributed to

SIADH, permanent central diabetes insipidus is observed in only 3% of cases [52, 53].

In summary, a patient with suspected pituitary apoplexy requires careful assessment of fluid and electrolyte balance. In addition, a complete blood cell count with differential should be obtained to assess for meningitis and for states of coagulopathy secondary to platelet dysfunction. Finally, a panel of hormone studies should be obtained to diagnose and monitor pituitary dysfunction. These should include random serum cortisol, free T4, TSH, IGF-1, and prolactin levels.

Emergency Department Management

Initial management of pituitary apoplexy in the emergency department should focus on supporting the patient's hemodynamic status and treating adrenal insufficiency (Fig. 17.7). The major source of morbidity and mortality associated with pituitary apoplexy is acute adrenal insufficiency from which early series of patients reported mortality close to 50% [2, 34]. However, in recent years there has been quite an improvement in outcomes associated with treatment of this condition largely attributed to improved ability to diagnose pituitary apoplexy with better imaging technology and to recognition and appropriate management of adrenal insufficiency.

The most important initial treatment of pituitary apoplexy and the associated cortisol deficiency is administration of glucocorticoids. After drawing blood for a baseline measurement of serum cortisol, a "stress" dose of 100 mg of hydrocortisone is administered intravenously in patients with suspected adrenal insufficiency. This is followed by a short course of high-dose hydrocortisone (50 mg intravenously at 6-hour intervals) with a subsequent slow taper based on the patient's clinical response. Patients are typically discharged on a maintenance dose of hydrocortisone (15–20 mg daily in divided doses) [18]. In addition to treating the adrenal insufficiency, in the acute setting, glucocorticoids reduce the swelling associated with the underlying tumor and hemorrhage. Thus they minimize the pressure in the sellar region and may lead to symptom improvement.

Intravenous fluid administration to maintain euvolemia and support blood pressure should be instituted. To minimize the amount of edema associated with the hemorrhage, normal saline or Ringer's lactate should be used. If the patient presents with hyponatremia, attention should be paid to the rate of sodium correction to ensure that it increases by 12 mEq/L or less in 24 hours [18]. Gradual correction helps to minimize the risk of central pontine myelinolysis, a devastating complication of sudden large shifts in serum sodium levels.

In patients with pituitary apoplexy who are hypertensive or who take anticoagulants or antithrombotic medications, the blood pressure should be controlled medically and the anticoagulant effects reversed [54]. This is relatively straightforward for patients on heparin or warfarin but more chal-

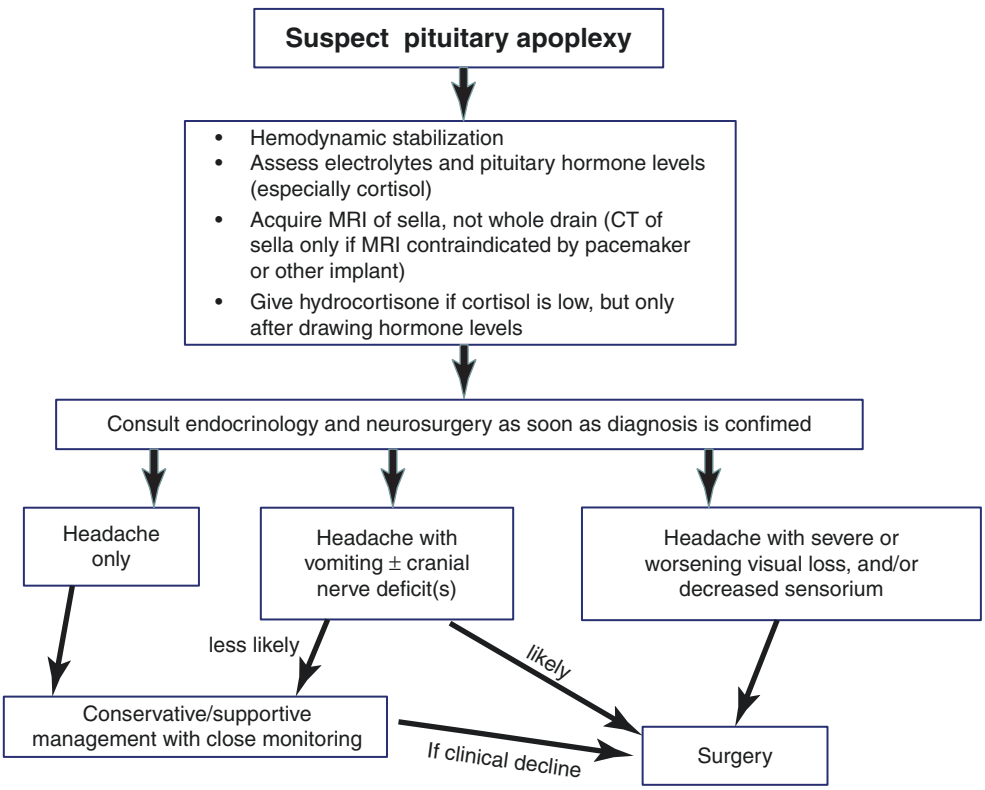

Fig. 17.7 Algorithm for decision-making when treating a patient for possible pituitary apoplexy

lenging for those on one of the direct oral anticoagulants now widely used for treating venous thromboembolism and for stroke prevention. These include the direct thrombin inhibitor dabigatran and the Xa inhibitors apixaban, rivaroxaban, and edoxaban. Reversal of the latter group requires either administration of prothrombin complex concentrate or andexanet alfa; dabigatran can be abrogated by idarucizumab (5 gm i.v. over 5 minutes), which binds it with high affinity [55].

Neurosurgical Management

There are no clear guidelines for definitive management of pituitary apoplexy. In a subset of patients managed conservatively, it is difficult to predict who will ultimately require a surgical intervention. No randomized controlled studies are available to provide evidence of differences in outcomes in conservative versus surgically treated patients. Although the question remains unanswered whether operative or nonoperative management is best, patients usually undergo surgery unless their symptoms are minor and no neurological deficits are present (see Fig. 17.7).

Traditionally, pituitary apoplexy has been treated surgically. In patients presenting with acute vision loss, worsening visual field deficit, or ophthalmoplegia, surgical intervention is indicated (see Figs. 17.4 and 17.5) [12, 50, 56]. The "pituitary apoplexy score" (PAS) introduced in 2011 can be used for monitoring patients for signs of deterioration [50]. It incorporates assessment of level of consciousness, visual acuity, visual field deficits, and presence of ocular nerve palsies. A PAS of 4 or greater, or an increasing score while the patient is under observation, may indicate the need for a surgical intervention [50, 57]. Furthermore, surgery should be offered to patients who have no improvement in their symptoms after 1 week of steroid administration [15, 58]. Recent surgical series show that endonasal transsphenoidal surgery for tumor removal and evacuation of hemorrhage provides prompt, effective, and safe decompression of sellar and parasellar structures and is associated with good recovery of vision and clearance of headache [59–61].

Recent retrospective case series demonstrate no difference in the visual and endocrine outcomes between patients treated conservatively and those who underwent surgery and thus make a case for conservative management of pituitary apoplexy [17, 51, 62, 63]. Indeed, some degree of slow shrinkage of tumor has been reported in 76% of patients followed without surgery [59]. These studies, however, suffer from a significant selection bias and do not have appropriately matched controls, since in most studies patients with larger tumors or more severe symptomatology undergo surgical decompression. One study examined the imaging characteristics of pituitary adenoma, including ischemic and hemorrhagic tissue, in an attempt to predict the likelihood of success of conservative management [58]. The presence of a single larger hypodense area within the tumor on a CT scan and early radiographic evidence of tumor involution may be associated with a higher likelihood of clinical resolution of pituitary apoplexy [58]. Regardless of the management strategy chosen, the outcome after treating pituitary apoplexy is excellent, as demonstrated in a recent retrospective cases series of 87 patients [56]. While 20% of patients were treated conservatively, there were no significant differences in outcome metrics between the two groups. Moreover, among those patients, one third presented with a significant alteration of level of consciousness but had an excellent recovery with conservative management [56].

One strong argument for conservative treatment can be made for hemorrhage into a prolactinoma given that medical treatment is the standard of care for that tumor subtype at present. Dopamine agonists are effective at reducing prolactin levels and at reducing the size of the tumor [64]. However, if such a patient presents with worsening vision caused more by the hemorrhage than the tumor volume per se, it is reasonable to consider prompt transsphenoidal decompression of the optic apparatus.

The endoscopic or microsurgical transsphenoidal approach is used most often for decompression of hemorrhage into a pituitary adenoma [34, 61, 65]. This surgery confers low morbidity and mortality for the patient and provides adequate decompression of the neurological structures of the sellar region. Furthermore, because this approach for the most part allows access to the adenoma itself, it allows the surgeon to address the primary lesion in addition to the hemorrhage.

Rarely, subarachnoid bleeding associated with pituitary apoplexy can provoke arterial vasospasm, which may lead to cerebral infarction if not controlled. Vasospasm can be diagnosed by transcranial Doppler or cerebral angiography and reversed by angioplasty directed at the affected vascular segment(s) [66]. As a patient with apoplexy severe enough to cause subarachnoid hemorrhage generally has a concomitant visual and hormonal loss, urgent transsphenoidal decompression is indicated with avoidance of hypotension, in conjunction with angioplasty.

In summary, no clear guidelines exist to determine the optimal management strategy for pituitary apoplexy. A multidisciplinary team involving an endocrinologist, neurosurgeon, and ophthalmologist is necessary to determine the optimal direction of care. Patients with minor symptoms of pituitary apoplexy, or those who have clinical improvement after the apoplectic episode, can be treated conservatively with excellent recovery. On the other hand, patients with visual compromise, significant visual field deficits, and ophthalmoplegia require surgical decompression of the sellar lesion via a transsphenoidal approach.

Outcomes and Follow-Up

The goal of treatment of pituitary apoplexy is to improve compromised visual acuity, reduce visual field defect, and enhance pituitary function. Loss of vision resulting from pressure on the optic nerves has traditionally been thought to be difficult to restore. Nevertheless, if surgical decompression is undertaken within 1 week of the event, there is significant improvement in visual acuity [12, 67]. The success rate is much lower when the surgical intervention is delayed, implying that prolonged compression of optic nerves ultimately results in permanent nerve damage.

In patients who present with minor visual symptoms such as a small field cut, conservative management demonstrated a comparable rate of symptom improvement, thus suggesting that conservative management with glucocorticoids is an alternative strategy [51]. The direct comparison of surgical versus medical management in pituitary apoplexy is complicated due to lack of appropriately matched controls in the studies.

In contrast to the improvement in the visual symptoms, pituitary function does not recover as well after apoplexy. Nevertheless, 50% of patients will have some improvement in pituitary function [19, 68], but 80% of patients will require long-term supplementation of at least one hormone, usually cortisol or thyroxine [12, 51, 62]. Overall, testosterone replacement is needed in 64% of patients [15]. On the other hand, central diabetes insipidus is relatively uncommon, and DDAVP replacement is required only in 20% of patients. Interestingly, the incidence of a need for DDAVP in the conservatively managed group of patients is low, while surgical decompression is associated with a higher rate of diabetes insipidus, observed in 23% of patients treated surgically [56]. Recovery from anterior pituitary insufficiency does seem to correlate somewhat with the prolactin level prior to surgery, with the best outcome in this regard seen when prolactin is ≥8.8 ng/mL [69]. That correlation makes sense as a low prolactin indicates a more profoundly damaged anterior lobe.

The pace and likelihood of improvement after resection of an apoplectic pituitary adenoma was nicely demonstrated by Zaidi et al. [70]. In their large surgical series, headache and loss of vision showed consistent resolution, whereas complete correction of ophthalmoplegia occurred in 83%; hormonal deficits recovered infrequently and typically required long-term supplementation. Ophthalmoplegia was the slowest to improve, with a mean time to recovery of 2.4 months, in contrast to the much faster mean times for recovery found with visual field deficits (8 days) and headache (2 days).

Summary

Pituitary apoplexy is a clinical syndrome associated with pituitary tumor hemorrhage that may result in visual acuity and field compromise, ophthalmoplegia, and pituitary dysfunction. Initial investigations should include a CT scan to detect the presence of acute blood, formal visual field testing, and an MRI scan to delineate further the size and extent of the adenoma and hemorrhage. A complete endocrine workup should be performed on admission, and acute cortisol deficiency should be corrected if present. Further management of a patient with pituitary apoplexy should include a multidisciplinary team consisting of a neurosurgeon, endocrinologist, and ophthalmologist, and a decision with respect to surgical versus conservative management should be made in a careful and nuanced fashion driven by the severity of the patient's symptoms, the degree of compression of the optic nerves and chiasm, and the size of the pituitary adenoma. Overall the outcomes of pituitary apoplexy are excellent.

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Spinal Cord Compression

18

Jayne M. Viets-Upchurch and Sorayah S. Bourenane

Case Study

A 73-year-old woman with a history of breast cancer presented to the emergency department (ED) for evaluation of bilateral lower extremity weakness and shaking. She was diagnosed with locally invasive, nonmetastatic breast cancer 6 months prior to her presentation. Treatment has been delayed due to endemic health concerns. In the interval, she received hormonal therapy in anticipation of surgical resection which was scheduled to take place in 2 days.

She reported a 3-week history of bilateral lower extremity weakness with a sensation that her knees were about to give out. Symptoms were intermittently and without warning. Although she has not fallen, her symptoms occur frequently enough that she quit taking her routine morning walks. Two weeks prior to her presentation, she developed bilateral hip pain that was sharp and shooting. It occurred at night and was described as nonradiating and 8/10 in severity. Three days prior to her presentation, she had a near-miss fall in her kitchen and now feels weak enough that she ambulates with a cane. For the past 2 days, her calf muscles felt tight bilaterally. She denies fecal or urinary incontinence and has no numbness or paresthesias. She has a headache she describes as "not bad." She has taken no medications for her symptoms, electing to treat them with breathing exercises, meditation, and rest.

She was evaluated at an urgent care facility in her hometown. The physician suggested she might have Guillain-Barre syndrome and offered no further evaluation or therapy. She traveled 1500 miles yesterday to arrive at your facility for her surgery day after tomorrow.

Aside from lower extremity ankle edema after air travel yesterday, her review of systems is otherwise negative. Her past history is notable for venous thromboembolism managed with IVC filter placement.

Her physical exam reveals a well-appearing woman. Her neurologic exam revealed normal strength and patellar reflexes with intact sensation, with no saddle anesthesia or clonus. Her gait is not tested due to the patient's sensation of instability. The remainder of her examination is unremarkable, with the exception of a firm tumor mass in the upper outer quadrant of the left breast. There is no apparent lymphadenopathy and only mild ankle edema.

Her laboratory evaluation reveals a normal CBC, metabolic profile, and no evidence of coagulopathy. A CT of the head is normal; however, an MRI of the cervical thoracic and lumbar spines shows evidence of metastases at T9 with circumferential epidural tumor burden compressing and deforming the cord. She has further osseous metastases at L5 with circumferential epidural tumor burden narrowing the canal and crowding the roots of the cauda equina.

Neurosurgery evaluated the patient in the ED. She had no bony impingement upon the spinal cord or thecal sac, and recommendations were given for radiation therapy. Radiation oncologic evaluated the patient and deemed her a suitable candidate for therapy.

The patient was admitted to the hospital and treated with steroids and analgesics. On restaging, a CT of the chest showed the known primary tumor with new invasion of the chest wall musculature as well as scattered pulmonary nodules too small to characterize. There was no lymphadenopathy. CT of the abdomen and pelvis revealed no clear-cut evidence of visceral metastases. Multiple bony lesions were noted. Nuclear medicine bone scan was notable for multifocal skeletal uptake consistent with metastases at T9, L5, left acetabulum, left femur, and left ischium.

Physical therapy was consulted. She was discharged home on hospital day 3 with improved symptoms. Outpatient

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follow-up was scheduled with physical therapy, relation oncologic, and breast medical oncologic.

Introduction

Traumatic spinal cord injury is a well-documented, devastating injury leading to sensory loss, paralysis, sphincter dysfunction, and protracted pain. The Centers for Disease Control and Prevention estimates that there are 12,000–20,000 such cases annually [1]. Malignant spinal cord compression (MSCC) is equally devastating and occurs at a similar rate to traumatic spinal cord injury [2]. Curative and life-prolonging treatments in cancer patients are expected to yield an increased incidence of the condition.

Cancer is the most common systemic disease affecting the spine [3]. MSCC presents as a true oncologic emergency resulting from tumor-related compression of the thecal sac and spinal cord [2, 4]. As with traumatic injury, untreated MSCC leads to paraplegia, incontinence, and permanent disability. It presents clinically in approximately 3–10% of cancer patients prior to death [5, 6]. Cancer patients have a median survival of 3–6 months from diagnosis of MSCC [5, 7, 8]. Once treated, 8–20% of patients experience recurrent compression either locally or at another vertebral level [9, 10].

The past several years have yielded significant advances in the diagnosis and treatment of this condition. Prompt recognition and treatment is essential to maintain mobility and neurological function. Any former or active cancer patient presenting with new or worsening back pain, even in the absence of neurological deficit, merits evaluation for spinal cord compression [11]. Individual risk assessment is necessary [12].

Epidemiology

Postmortem studies suggest that MSCC is present in up to 36% of cancer patients [13, 14]. In a US nationwide study of 15,367 cases of MSCC, the mean age at hospitalization was 62 years [6]. Men outnumber women nearly two to one, with only 37.5% of cases occurring in women. In approximately 20% of cases, MSCC is the initial presentation of cancer [8, 15]. Increasing cancer prevalence, coupled with prolonged life expectancy of diagnosed patients, is anticipated to drive the incidence upward.

Prevalence of MSCC varies depending on tumor type. Cancers of the breast, lung, and prostate each account for 15–20% of cases. Renal cell carcinoma accounts for an additional 5–10%. Multiple myeloma and lymphoma are the most frequent liquid tumors associated with MSCC, each contributing 5–10% of cases [2, 6, 16]. MSCC affects up to 15% of myelomas [5, 6] and 13% of lymphomas [6]. In patients with prostate cancer, 5.5% develop MSCC [6]. In contrast, it occurs in only 0.2% of pancreatic cancers [5]. In children, the most commonly associated malignancies are sarcoma, neuroblastoma, germ-cell tumor, and Hodgkin lymphoma [2, 16].

The most common location of MSCC is the thoracic spine (70% of cases); 20% of cases occur at the lumbosacral level and 10% in the cervical region [2]. It is hypothesized that this pattern represents the primary tumor's lymphatic drainage. Accordingly, metastases from breast and lung cancers tend to be found in the thoracic spine. Pelvic and intra-abdominal malignancies most commonly migrate to the lumbar spine. Multiple, noncontiguous spinal epidural metastases were noted in 32% of patients who underwent complete imaging of the spine [17]. Among those, two-thirds have multicentric disease affecting more than one region (cervical, thoracic, and lumbar) of the spine [18].

Historical factors that predispose the patient to MSCC include known metastatic disease at the time of cancer diagnosis and known vertebral metastases.

Pathophysiology

Most cases of MSCC are epidural in origin, arising from the vertebral column in 85% of patients [2]. The marrow of the vertebral body provides fertile ground for circulating tumor cells. Their growth eventually replaces the marrow and invades into the canal through thrombosed venous plexuses. These events appear to occur independently of bony destruction [19]. Epidural spread may also occur by direct tumor extension or by direct deposition of tumor cells into the epidural space [16].

Ultimately, neuronal injury is thought to involve vasogenic edema [20] leading to ischemia [19], presumably through venous infarction, but there has been debate regarding this last phenomenon [21]. In cases of paralysis, demyelination is evident [21].

Clinical Presentation

History

Presenting symptoms of MSCC can be motor (weakness, paraplegia), sensory (pain, numbness, neuropathy), and/or autonomic (incontinence). Symptoms vary based on the location of the metastatic lesion; however, they are a poor indicator of the level of involvement [18].

Although it is nonspecific, pain is the primary complaint in 83–96% of those with MSCC [22, 23]. Pain can be referred, local, radicular, or a combination of all three [24].

Misdiagnosis is a common issue in the ED setting. In an interesting retrospective study of 63 patients with spinal cord compression from a variety of causes (only 10 were due to cancer), 18 (29%) were misdiagnosed [25]. Consequently, there was a significant delay in diagnosis despite obvious neurological deficits at presentation. Highlighting this historical delay, back pain is present for a median of 62 days prior to treatment of MSCC [26].

Patients may report pain in a band-like distribution. It is generally described as sharp, shooting, or deep [11]. As with mechanical causes of back pain, the pain associated with MSCC may worsen with weight-bearing loads, which bring pressure to bear on the vertebral column [27]. Other common precipitating factors include coughing, bending, and sneezing [11]. Twenty percent of patients report that rest in a supine position exacerbates symptoms and often disrupts sleep [3, 11]. These patients frequently sleep in an upright position.

Weakness follows pain with an estimated 35–85% of patients endorsing the symptom [28]. Patients presenting with radiculopathy are symptomatic an average of 9 weeks prior to diagnosis [29].

Early studies showed ataxia in up to 67% of patients with nearly 65% of those having profound motor deficits that prevented walking [22]. Perhaps as a result of heightened awareness, a more recent study of patients receiving radiation therapy showed 67% of patients were ambulatory (although 28% required assistance) [30]. Loss of sensation, dense paraplegia, and incontinence are late findings and signal some degree of permanent disability [22].

Because of its high specificity (98%), any cancer patient with new back pain should be considered to have metastasis until proven otherwise [3]. Because cord compression is an evolving condition, a patient with previously stable back pain may present with recently worsening symptoms.

Physical Examination

Spinal tenderness may be present overlying the level of metastatic deposit. Nonetheless, it is difficult to thoroughly assess the location of MSCC lesion on the basis of examination alone. Pain in the thoracic spine and abnormal gait are suggestive of cord compression [31]. However, the absence of these findings is not sufficient to rule out the disease.

Documentation of a detailed physical examination is essential. Serial exams are frequently required, and a thorough neurologic exam, including sensation, strength, and reflexes, should be carefully recorded upon presentation.

Patients with cervical spine tenderness or symptomatology should be immobilized and placed in a Philadelphia collar until stability of the area can be assessed. Likewise, if spinal instability is suspected, range-of-motion testing is contraindicated, and the patient should be immobilized.

Table 18.1 Levels of disability according to Frankel et al. [32]

Frankel grade	Motor	Sensory
A	Complete paresis	Insensate
B	Complete paresis	Sensation preserved
C	Incomplete but nonfunctional	Sensation preserved
D	Functional but symptomatic	Sensation preserved
E	Normal	Normal

Hyperreflexia and an upward-going Babinski reflex are common findings [31]. Weakness and paraplegia are late findings. Decreased rectal sphincter tone and urinary incontinence are indicators of poor outcome. A bedside bladder scan may be useful for documenting post-void residual to assess for evidence of urinary retention.

Degree of disability is typically described using the Frankel grading scale [32]. This scale, established in 1969, classifies patients according to five levels (A through E) with A being complete loss of both motor and sensory function and E being normal (Table 18.1).

Imaging

Advanced imaging is essential to delineate the extent of disease. By themselves, plain films of the spine are of little value in diagnosing the condition. Approximately 26–29% of metastatic deposits are occult on plain film X-ray [8, 14]. Furthermore, given the prevalence of osteoarthritic changes of the spine in adult patients, such plain films may offer false reassurance as to the etiology of the pain.

Prior to the 1990s, spinal cord compression was diagnosed by myelography [33]. Fortunately, this invasive and uncomfortable procedure has largely been supplanted by magnetic resonance imaging (MRI) (Fig. 18.1) [18].

While gadolinium-enhanced MRI can help to determine intradural tumor or leptomeningeal disease, it is not required for cord compression studies. Unenhanced MRI is equal to myelography in detecting epidural disease and is more sensitive at detecting vertebral metastasis [34], justifying its use and reducing procedure time compared to gadolinium-enhanced studies.

Computed tomography (CT)-guided myelography is of value for patients unable to tolerate MRI [35]. If both CT and MRI are unavailable, bone scintigraphy in combination with plain films may be of use [33].

Imaging studies should include the entire spine, not just the perceived area of pain. Up to 31% of patients have multilevel disease [17]. Sensory deficits and mechanical pain may be present 2–4 vertebral levels away from the actual lesion [31].

If MRI suggests cord compression, severity can be graded using the Epidural Spinal Cord Compression scale described by Bilsky [36]. This 6-point scale rates the degree of cord compression between 1 and 3 (with 3 being the most severe) based on the level of cord impingement (Fig. 18.2) [37]. A recent trial confirmed its continued utility for enhancing agreement and clarity of communication among clinicians [38].

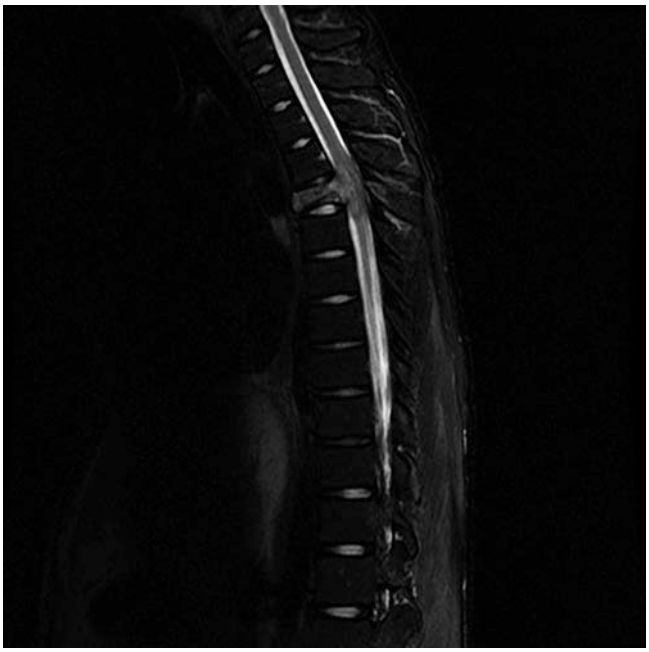

Fig. 18.1 A 16-year-old female with ovarian cancer and spinal cord compression at the level of the third thoracic vertebra

Management

The goal of therapy is symptom control and preservation of function. This requires a multidisciplinary approach involving nursing, medical oncologic, neurosurgery, and radiation oncologic services.

Nursing Efforts

Upon diagnosis and initiation of therapy, serial neurological evaluations should be undertaken. Neuro-vital signs should be scheduled to coincide with other nursing efforts to minimize patient discomfort and ease the burden of care. Patients with involvement of the cervical spine should have a Philadelphia collar placed until spinal stability has been confirmed. Strict bed rest (including logroll and bedpan use) should be instituted if there is suspicion of spinal cord instability.

In the United Kingdom, the National Institutes for Health Care Excellence guidelines recommend that all patients with suspected cord compression be maintained in a flat position [29]. Other authors do not believe that strict bed rest is necessary. Proponents of this theory believe that MSCC is inherently different from that caused by trauma. Authors supporting this position contend that the increased incidence of deep vein thrombosis, infection (particularly from the respiratory and urinary tracts), and decubitus ulcers outweigh the benefit of bed rest.

There is a lack of data or randomized controlled trials to strongly support either position [39]. A recent systematic review of non-pharmacological interventions in spinal cord

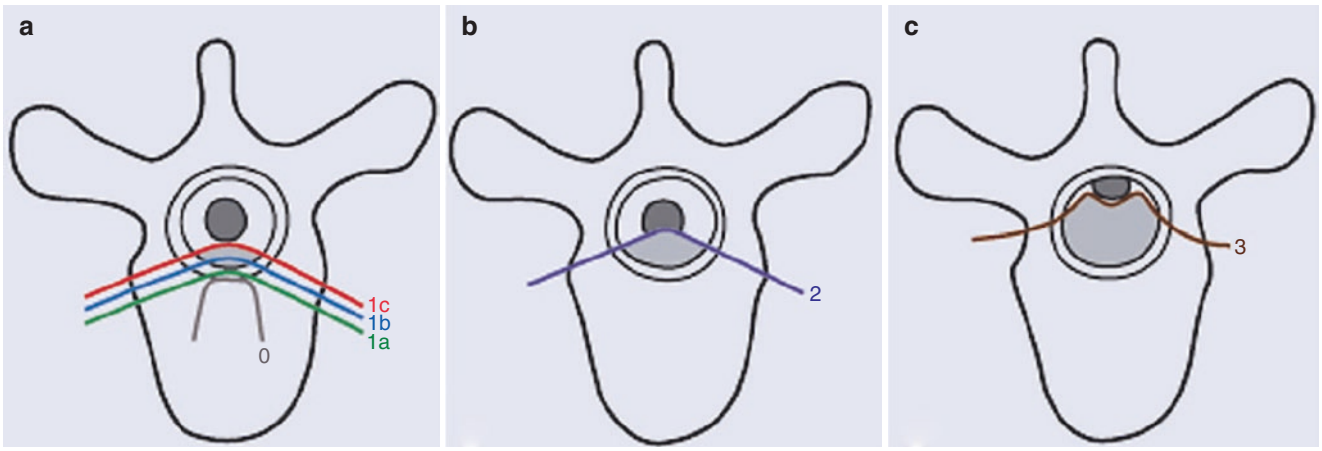

Fig. 18.2 Schematic representation of the 6-point ESCC grading scale. A grade of 0 indicates bone-only disease; 1a, epidural impingement, without deformation of the thecal sac; 1b, deformation of the thecal sac, without spinal cord abutment; 1c, deformation of the thecal sac with spinal cord abutment but without cord compression; 2, spinal cord compression but with CSF visible around the cord; and 3, spinal cord compression, no CSF visible around the cord. (From Bilsky et al. [37], with permission Elsevier)

compression found that while supine positioning is extremely important in other causes of spinal cord compression, it seemed excessive in MSCC patients, although again, the quality of the data was poor [40]. Patient performance status and preference should be taken into consideration as those with good functional status may be quite resistant to bed rest, particularly if it worsens their symptoms.

Medical Therapy

The mainstay of medical therapy is treatment with corticosteroids [4]. Unless contraindicated, they are recommended for all patients, particularly those with neurological deficits. Initial trials demonstrated that corticosteroids improve functional status, as well as symptoms, in MSCC.

Controversy exists regarding the effective dose. A randomized, controlled trial by Sorensen et al. evaluated functional outcomes in 57 patients who received radiotherapy in conjunction with high-dose versus no corticosteroids as adjunctive therapy. Fifty-nine percent of patients in the dexamethasone group were ambulatory 6 months after treatment compared to 39% in the group who did not receive steroids [41].

More recent studies have shown similar results with lower-dose corticosteroids [42]. A recent systematic review by Kumar suggests a loading dose of 10 mg of intravenous dexamethasone followed by 16 mg per day orally in two to four divided doses [4, 5, 43, 44]. In patients with recent-onset neurological deficits, higher doses may be considered [4]. National guidelines in both Canada and England now recommend more moderate dosing.

Corticosteroids are associated with psychosis, gastric ulceration/perforation, rectal bleeding, and hyperglycemia. Care should be taken to mitigate against these effects. Steroids should be weaned as early as tolerated and gastrointestinal prophylaxis should be initiated. Special attention should be given to glucose control (particularly in patients with preexisting diabetes). While not typically of use in the ED, chemotherapy is of value in longer-term management. In particular, seminomas, myeloma, and lymphomas may show a dramatic response to treatment [45–47].

Surgical Therapy

Overall, decompressive surgery is indicated in 10–15% of MSCC cases [48]. Surgical evaluation is required in cases of spinal instability, direct cord compression due to a bony fragment, and impending sphincter dysfunction. Unknown primary tumors will require biopsy even if full resection is not possible. Patients not responding to radiotherapy or those who have previously received radiotherapy may benefit from surgical intervention [20]. Radoresistant tuores, including sarcoma, melanoma, GI tumors, lung, renal and thyroid, are more likely to require surgical intervention [49].

The Spinal Instability Neoplastic Score (SINS) developed by Fisher et al. is the most frequently used tool to determine patients that will require surgical stabilization. The scale assigns a score between 0 and 18 to metastatic deposits. Six elements are considered, including lesion location, the degree of pain, type of lesion, radiographic spinal alignment, degree of vertebral body collapse, and the presence of involvement of the posterolateral spinal elements. Scores of less than 6 are generally considered stable. Those greater than 13 are deemed unstable and likely to require surgical intervention. Indeterminate lesions graded 7–12 require further evaluation [50] (Table 18.2).

Patients with good functional status, limited disease, and a life expectancy greater than 3–6 months may benefit from surgery [51]. Those with paraplegia of less than 48 hours duration may experience a degree of functional restoration. In a recent study, 101 patients presenting with neurologic symptoms underwent decompressive laminectomy. 74% showed improved motor function and 51% had regained the ability to walk at discharge [52].

Previously, laminectomy was the primary surgical option available. In many cases, it provided suboptimal results. Over

Table 18.2 Spinal Instability Neoplastic Score (SINS) System (From Fisher et al. [50], with permission Wolters Kluwer Health)

Component	Score
Location	
Junctional (occiput–C2, C7–T2, T11–L1, L5–S1)	3
Mobile spine (C3–6, L2–4)	2
Semi-rigid (T3–10)	1
Rigid (S2–S5)	0
Pain relief with recumbency and/or pain with movement/loading of the spine	
Yes	3
No (occasional pain but not mechanical)	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement of the spinal elements (facet, pedicle, or CV joint fracture or replacement with tumor)	
Bilateral	3
Unilateral	1
None of the above	0

the past two decades, significant improvements have been made. New surgical techniques including circumferential decompression of the spine with anterior posterior surgery stabilization have advanced the care of these patients [53].

Minimally invasive procedures, in conjunction with stereotactic body radiation therapy, have shown promise in the management of MSCC [54]. Although not routinely used, vertebroplasty or kyphoplasty has been shown to be effective for management of pain associated with pathologic compression fractures. Some authors have recommended kyphoplasty with stabilization. Chen reported excellent results in a study of 282 patients undergoing percutaneous kyphoplasty for metastatic disease. Patients were followed as far out as 15 months and reported decreased use of analgesia as well as improved quality of life and Karnofsky performance scores [55]. Similarly, in a study of 50 patients with spinal metastasis, Kwan found minimally invasive stabilization with percutaneous screws provided adequate relief of symptoms, with an associated improvement in Frankel score [56]. In a study specific to patients with MSCC, Chen found kyphoplasty with short instrumentation provided equivalent results to more traditional long stabilization. Moreover, there was less blood loss and fewer complications [57].

Prior to any surgical procedure, any coagulopathy should be corrected, and thrombocytopenic patients should receive platelet infusion. A recent review found post-operative complications are common. These include wound infection/dehiscence, pneumonia, pleural effusion, respiratory failure, pulmonary embolism, venous thrombosis, cerebral spinal fluid leak, urinary tract infection, and instrument failure [58].

Radiotherapy

The combination of surgery with radiotherapy has been shown to improve outcomes [59]. Whether for therapeutic or palliative intent, radiotherapy is provided to virtually all patients.

Tumors such as leukemia, lymphoma, and germ-cell tumors are particularly responsive to radiotherapy. Breast, prostate, and ovarian cancers have intermediate sensitivity [49].

Issues regarding duration and dosing depend on intent of therapy and must be individualized to the patient. While guidelines have been recommended, there are few randomized, controlled trials to clarify specific regimens [60].

Generally speaking, patients with a favorable prognosis will benefit from longer courses of therapy [61, 62]. End-of-life patients with a poor prognosis are typically treated with a single-dose regimen [61, 63]. These regimens provide similar symptom control as fractionated regimens but with an increased incidence of local recurrence [63–65]. A recent systematic review and meta-analysis showed no difference in survival or motor function between patients receiving short- versus long-course radiotherapy [66]. Patients experiencing local recurrence may be candidates for re-irradiation [48, 67].

While standard of care currently involves a combination of medical, surgical, and radiation therapies, recent advances in radiation oncologic underscore the increased impact of the specialty. Rades et al. showed promising results with radiation alone in treatment of myeloma [68]. Another study suggested that radiotherapy alone constitutes sufficient therapy in neurologically intact patients [69].

Stereotactic body radiation therapy (SBRT) has shown potential for treating metastatic bone disease in the spine. It has the ability to provide large doses of radiation to a highly select area providing local control of even radioresistant tumors. However its use in metastatic spinal cord compression remains limited at this time [70]. While a recent consensus study suggests that SBRT is contraindicated in cord compression [71], a new study by Ghia et al. found that it may be beneficial in select, inoperable patients [72].

Special Considerations

In spite of improved surveillance and diagnostic practices, 20% of MSCC occurs in patients without a known malignancy. A patient without a biopsy-confirmed cancer diagnosis in need of corticosteroid treatment presents a dilemma. If there is any question regarding the nature of the lesion, tissue diagnosis must be obtained without delay.

Steroids are used with curative intent in treatment of plasmacytomas, thymomas, lymphomas, multiple myeloma, and germ-cell tumors [45]. In these circumstances, corticosteroids given before tissue samples are obtained may cause regression of disease, hindering diagnosis and complicating delivery of definitive chemotherapy [73, 74]. In the absence of neurological deficit, corticosteroids may be withheld pending consultation with neurosurgery and oncologic.

Cancer patients are at increased risk of recurrent malignancy. Overall, cancer survivors have a 14% higher risk of developing a new malignancy than the general population [75]. In fact, second primary malignancies accounts for 16% of new cancer diagnoses [76].

The etiology of second primary malignancy varies. Treatment-related secondary cancers are well-documented complications of chemotherapeutic, hormonal, and radiation modalities. Familial cancer syndromes result in multiple primary cancer sites. Shared risk factors and lifestyle choices such as tobacco and alcohol use and sun exposure contribute to development of second primaries. Cancer survivors who are thought to have no evidence of disease may be experiencing either recurrent disease or the initial manifestations of a second primary process.

Prevention

Patient education is of primary importance. Lu et al. found that only 54% of patients were aware that back pain should be reported to their physician [31]. Delays in diagnosis and treatment are common and well described in the literature [26]. Patients should be instructed to call their physician within 24 hours of the development of any new or worsening back pain and should be advised to seek immediate care if they develop any neurologic symptoms.

Bisphosphonates have been shown to be effective in controlling symptoms from and prevention of skeletal metastases in breast cancer. However, they were not shown to delay development of MSCC [77, 78].

To facilitate appropriate and prompt management of MSCC, hospitals and treating physicians should develop diagnostic algorithms to minimize delays in referral to a comprehensive center for further treatment.

Prognosis

MSCC can be treated successfully; nonetheless it is associated with a poor outcome in most patients. It is evidence of an uncontrolled and aggressive disease process. Although lymphoma and myeloma patients fare better than other patients, the average lifespan after development of MSCC is less than 6 months [5, 7, 8]. Patients with limited disease and good functional status may survive for years [53].

A consensus study including 60 international experts included metastatic spinal cord compression among 11 major criteria for referral to palliative care [79]. Certainly, patients with poor functional status and those with end- or late-stage disease should be referred to palliative care for the management of symptoms [80].

Given the poor prognosis of MSCC in general, end-of-life discussions are warranted. In a retrospective study of 88 patients with MSCC, "do not resuscitate" orders were in place in only 9% of the patients during their hospital admission [81]. Improved doctor-patient communication in the ED setting will facilitate the patient's coping with future losses.

Conclusion

Metastatic spinal cord compression is an uncommon but well-established consequence of advanced cancer. It affects both survivors and patients with active disease. Patient education is a key factor in early diagnosis. It may represent the first manifestation of cancer (or a second primary cancer in the case of long-term survivors). The primary complaint is typically back pain. Neurological deficits are associated with a poor outcome. The diagnosis requires a high index of suspicion and MRI is the imaging modality of choice. Definitive treatment requires cooperative efforts by medical, surgical, and radiotherapeutic disciplines. Symptom control and maintaining (or regaining) functional status are of paramount importance. While the best predictors of outcome are ambulatory and functional status at the time of diagnosis, MSCC is generally associated with a poor prognosis. Palliative care and end-of-life issues should be considered with all patients who develop the condition.

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Head and Neck

19

Ray Y. Wang, Eugene L. Son, Clifton D. Fuller, and Neil D. Gross

Introduction

Head and neck cancer is the fifth most common cancer worldwide with almost 53,000 people diagnosed each year in the United States [1]. These include malignancies of the upper aerodigestive tract (UADT), which begins at the lips and nose and extends to the mucosal surfaces of the cervical trachea and esophagus. The UADT includes the oral cavity, oropharynx, hypopharynx, larynx, nasal cavities, and paranasal sinuses. The most common malignancy of the UADT is squamous cell carcinoma of the head and neck (SCCHN), making up over 97% [2]. For simplicity, SCCHN will be the primary focus of this chapter. Other pathologies in the head and neck including carcinoma of the major and minor salivary glands, thyroid, and skin will not be covered.

Patients with SCCHN may present to the emergency department (ED) with a variety of complaints at any point in the course of their disease, from initial diagnosis to years after completion of therapy. Patients presenting on an emergency basis represent 7% of all referrals with dysphagia, stridor, and neck mass being the most common chief complaints [3]. Also typical, pain and gastrointestinal complaints were the most common presenting symptoms among patients with SCCHN in a population-based study from Taiwan [4]. The symptom profile of patients presenting may vary over their treatment course, although pain is a consistent symptom [5]. In one prospective cohort study, patients presenting during or soon after treatment presented most frequently with gastrointestinal complaints while those presenting >6 months after treatment initiation were most likely to present with pain [5].

Uncontrolled SCCHN can result in life-threatening emergencies, principally from compromise of the airway and/or bleeding. Patients with undiagnosed SCCHN may present to the ED in distress because the SCC of the base of tongue and larynx can grow to be large with relatively few symptoms [6]. In this chapter, we discuss acute management of the airway in patients with SCCHN including in the context of COVID-19. We also review the management of emergent bleeding in patients with SCCHN. Finally, we cover common complications from the treatment of SCCHN and end with clinical pearls for acute management of SCCHN in the ED.

Case Discussion

A 59-year-old man with a history of recurrent oropharyngeal squamous cell carcinoma presented to the ED for evaluation of bleeding from his neck and mouth. A few hours prior to presentation, he suddenly developed severe bleeding ("several cupsful") externally from his tumor as well as from his oral and nasal cavity. This resolved spontaneously prior to arrival in the emergency room.

He has a complex oncologic history including squamous cell carcinoma of the base of tongue initially treated with concurrent chemoradiation approximately 2 years prior to the presentation followed by partial glossectomy, neck dissection, and free flap reconstruction for recurrence a few months later. He again was noted to have recurrence with extensive progression involving the neck soft tissues with multiple pharyngocutaneous fistulae.

On examination, he was afebrile, tachycardic (HR 110s) but normotensive. He was breathing well on room air without stridor though with audible pharyngeal secretions. He had extensive tumor involvement of the anterior neck with

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multiple fistulae with dark clot but no active bleeding. He also had post-treatment sequelae including radiation fibrosis with limited neck range of motion and trismus from his prior surgery and reconstruction. Flexible fiberoptic nasopharyngoscopy demonstrated a large blood clot at the left base of tongue at the site of his recurrence with marked supraglottic edema.

Given the potential for acute airway compromise due to bleeding from his pharyngeal tumor, he was taken emergently to the operating room where he underwent awake transoral fiberoptic intubation followed by tracheostomy. After securing the airway, a CT angiogram of the head and neck was obtained which did not demonstrate obvious extravasation. He was then taken by interventional radiology for angiography and a pseudoaneurysm of the left facial artery was noted. This was managed via selective arterial embolization. The patient demonstrated no additional bleeding after the procedure.

Airway Management

Airway obstruction due to SCCHN affects up to 80,000 patients annually, with most patients presenting to the ED for acute care [7]. Ideally, planning for airway management in patients with SCCHN should occur well before an emergency. This may include prophylactic tracheostomy. In addition to acute airway obstruction, SCCHN patients have increased rates of aspiration pneumonia because of dysphagia and difficulty handling even normal oral secretions [8]. The 1-year and 5-year incidence of clinically meaningful aspiration in SCCHN patients is 15.8% and 23.8%, respectively, with 84% of these patients requiring hospitalization [9]. For the purposes of this chapter, we have divided the airway into *unsecure* and *secure*.

Unsecured Airway

Undiagnosed SCCHN can lead to signs of obstruction before causing other symptoms such as pain [10]. Metastatic cervical adenopathy can also cause obstructive lymphedema and direct extrinsic compression of the airway. Patients with undiagnosed SCCHN may present with orthopnea, hoarseness, dysphagia, odynophagia, and hemoptysis [10]. Stridor and/or drooling can be signs of an unsecured airway.

In stable patients, a contrasted computed tomography (CT) of the head, neck, and chest can be performed quickly to assess the location and extent of the obstruction [10]. This imaging study provides important staging information if malignancy is confirmed. Flexible fiberoptic laryngoscopy (FFL) is a critical tool for assessing the airway and is the most direct method to evaluate for impending obstruction

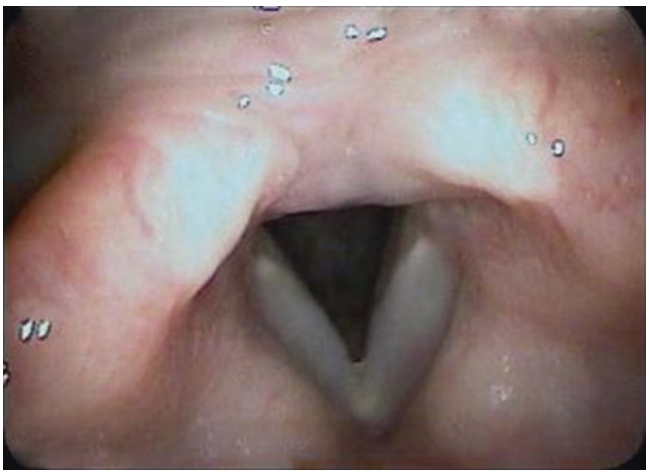

Fig. 19.1 Flexible fiberoptic laryngoscopy demonstrating normal larynx

[10] (Fig. 19.1). Skilled management of the FFL is important for evaluating a potentially tenuous airway. Topical administration of local anesthetic such as lidocaine and topical decongestants (oxymetazoline or phenylephrine) to the nasal cavities may make FFL more tolerable and potentially safer (see Fig. 19.1). Management of a suspected unsecure airway starts with optimal positioning to make the patient as comfortable as possible. Administration of supplemental oxygen may be helpful but should be used with caution in patients with uncompensated chronic obstructive pulmonary disease (COPD). Administrating nebulizers and steroids are unlikely to improve the airway but may be useful in temporizing the patient. The use of Heliox, a mixture of helium and oxygen, has been described in the acute management of patients with an unsecure airway. The decreased viscosity of Heliox can temporarily improve airflow and reduce stridor. Because it is an inert gas, it can assist in temporizing an unsecure airway, but it may not be readily available in the ED [11].

SCCHN patients with acute respiratory failure from an unsecure airway should be managed expeditiously. Transoral intubation is preferred if FFL predicts that direct visualization of the endolarynx can be achieved safely. The use of laryngeal mask anesthesia (LMA) is not recommended in these cases because of likely distortion of the normal anatomy. In cases where oral intubation is not possible (e.g., obstructing mass, trismus), awake fiberoptic transoral or nasotracheal intubation is usually the next best option. Nasotracheal intubation is preferred over awake fiberoptic oral intubation to decrease patient gagging but requires a unique skill set and is probably best performed by experienced anesthesiologists or otolaryngologists. Successful intubation can avoid an emergent surgical airway and allow a controlled environment for formal tracheostomy [6]. SCCHN involving the larynx is most likely to result in an unsecured airway (Fig. 19.2). Intubation of a patient with

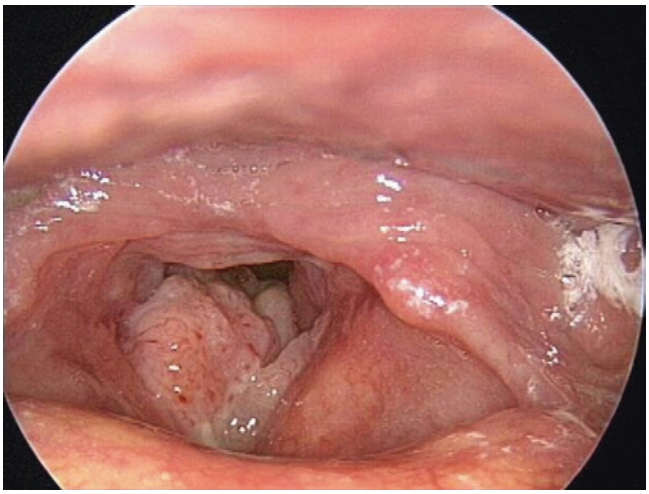

Fig. 19.2 Flexible fiberoptic laryngoscopy demonstrating obstructing mass of the larynx. Note loss of visualization of the vocal cords and the markedly decreased diameter of the airway

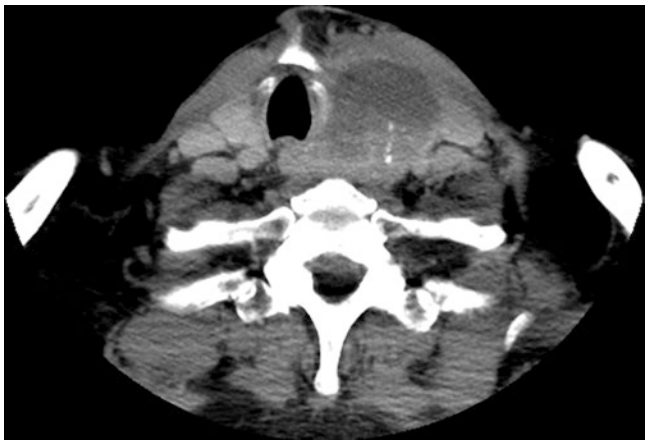

Fig. 19.3 Axial computed tomography (CT) of the neck demonstrating a left-sided thyroid mass with invasion into the cricoid cartilage. This patient presented with a paralyzed ipsilateral vocal cord secondary to involvement of the recurrent laryngeal nerve

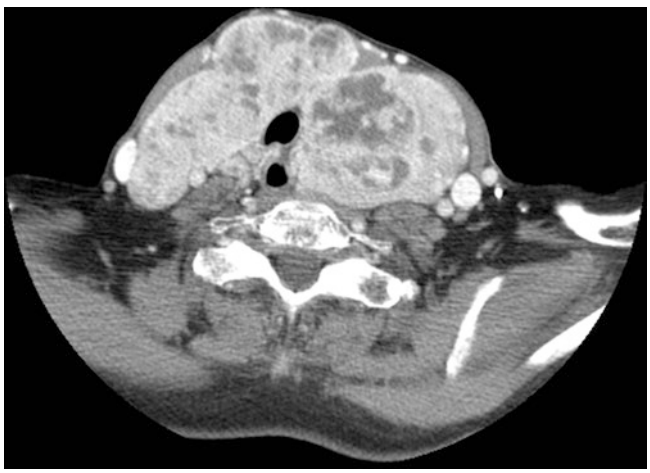

Fig. 19.4 Axial computed tomography (CT) of the neck demonstrating a large goiter with narrowing of the airway but no obstruction

locally advanced SCC of the larynx can be hazardous because of the distorted anatomy and risk of bleeding during laryngoscopy. In these cases, the airway is best managed in the operating room by an experienced anesthesiologist and/or otolaryngologist.

If attempted intubation is deemed unsafe or unsuccessful, then a surgical airway via cricothyroidotomy or tracheostomy should be performed. Awake tracheostomy can be performed under local anesthesia in select SCCHN patients with an unsecure airway. This is best performed in the operating room. If an urgent airway is needed (e.g., acute obstruction) then a "slash" cricothyroidotomy should be performed. A vertical incision is usually advised in this setting, as a midline dissection is critical to minimize bleeding from the paired paramedian anterior jugular veins and allowing for identification of the airway across a vertical range. In cases where the trachea is deviated, a needle on a saline-filled syringe with negative pressure can be used to locate the trachea by visualization of air bubbles [12]. Transtracheal catheterization has also been described if cricothyroidotomy or tracheostomy cannot be performed [13].

Some head and neck cancers, particularly thyroid cancers, can cause paralysis to one or both of the vocal cords via direct involvement of the recurrent laryngeal nerves (Fig. 19.3). This is in contrast to large goiters that can distort the airway over time but rarely cause respiratory distress (Fig. 19.4). Acute bilateral vocal fold paralysis, either by direct tumor involvement or iatrogenic after thyroid surgery, can cause respiratory distress marked by stridor. These patients typically require intubation and subsequent tracheostomy if possible. Anaplastic thyroid cancer is the prototypic malignancy to cause acute airway obstruction by direct tracheal involvement, recurrent laryngeal nerve involvement, or both. Fortunately, anaplastic thyroid carcinoma comprises only 1.7% of all thyroid cancers [14]. Management of the airway in patients with anaplastic thyroid cancer is complex and controversial particularly given the dismal prognosis associated with the disease [15]. For this reason, current American Thyroid Association guidelines recommend against elective tracheostomy [14].

Secured Airway

The airway management of SCCHN patients with a tracheostomy or laryngectomy stoma requires some familiarity with changes to the anatomy with these procedures. Most clinicians are familiar with tracheostomy patients whereby the oral cavity, oropharynx, and larynx are bypassed by a tube directly into the trachea. In contrast, laryngectomy

patients are obligate "neck breathers" with no remaining connection between the mouth and trachea.

As with all patients presenting with respiratory distress, conservative measures should always be initiated including oxygen administration. However, nasal cannula or facemask administration may be ineffective if the patient breathes through a surgically created stoma in the neck. Oxygen can be applied to both the face and stoma for tracheostomy patients but only the stoma for laryngectomy patients. Fiberoptic tracheoscopy can be a valuable tool to rule out a proximal obstruction or false passage of the tracheostomy tube. The scope can be introduced inside the stoma or tube in place to visualize the carina and proximal mainstem bronchi.

SCCHN patients with a tracheostomy are at risk of life-threatening complications, including bleeding and tube dislodgement with airway obstruction and death [16]. There are known late complications of tracheostomy in up to 65% of patients including possible granulation tissue formation, tracheomalacia, tracheoinnominate fistula (TIF), tracheoesophageal fistula, pneumonia, and aspiration [17]. These potential complications from tracheostomy tubes are important to recognize in the acute setting.

Patients can present to the ED with airway obstruction despite having a tracheostomy tube. If a tracheostomy tube becomes dislodged, then every effort should be made to replace the tube as the stoma can close substantially in a matter of hours. If the original tracheostomy tube is too large for the tracheostomy stoma at the time of replacement, then the tract can be dilated with a nasal speculum or a smaller tube can be inserted. An endotracheal tube can even be used temporarily to secure the airway if needed. However, it is important to keep the cuff visible near the stoma to avoid a mainstem bronchus intubation.

Mucous plugging of a tracheostomy tube can cause acute airway obstruction and death. For this reason, most commercially available tracheostomy tubes have an interchangeable inner cannula. Patients need appropriate humidification of air and frequent suctioning of the tube to prevent mucous build-up. Applying small amounts of saline and suctioning with a soft flexible catheter can soften and remove hardened mucous.

There are special considerations regarding the emergency management of laryngectomy patients. A survey of members of the National Association of Laryngectomy Clubs in the United Kingdom underscored concerns regarding the quality of care they receive in the emergency setting [18]. It is incumbent upon emergency physicians to be familiar with the anatomy of patients after laryngectomy and the common complications that can occur. For example, it is important to realize that either a standard tracheostomy tube or more customized laryngectomy tube may be used for comfort or to stent the stoma. In the superior posterior wall of the trachea, a tracheoesophageal puncture (TEP) device may be present which provides a one-way valve for air to flow from the trachea into the esophagus for speech (Fig. 19.5). If a patient requires mask ventilation, then the laryngectomy patient should be intubated through the stoma either with a cuffed endotracheal or tracheostomy tube past the TEP, if present. The rate of 30-day unplanned readmission independent of complications following laryngectomy ranges from 26.5% to 42% [19]. Most of these patients present for stomal or TEP complications [19]. Non-humidified air entering the proximal trachea can cause thickened respiratory secretions that are difficult to clear. These secretions can dry into dense circumferentially crusts which can obstruct the airway. Post-laryngectomy patients also frequently come to the ED for TEP dislodgement. When this happens, a chest film must be taken to rule out aspiration of the device as aspiration has been reported to occur in up to 13% of patients [20]. If the patient comes with a dislodged TEP device in hand, replacement can be difficult without extensive experience and specialized tools. Replacement of the TEP is usually done by a speech and language pathologist or otolaryngologist. If replacement is not an immediate option, then placement of a temporary red rubber catheter through the TEP site can help prevent aspiration and closure of the puncture itself.

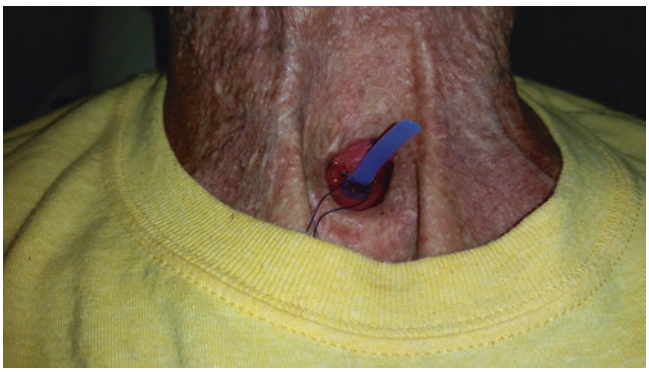

Fig. 19.5 Laryngectomy stoma with blue tracheoesophageal puncture (TEP) voice prosthesis in place

Considerations During the SARS-CoV-2 (COVID-19) Pandemic

The SARS-CoV-2 (COVID-19) pandemic introduced significant new challenges for providers caring for head and neck cancer patients. Given the anatomic location of SCCHN, care for these patients places providers at high risk for transmission due to the need to examine the UADT. Furthermore, cancer patients may be at increased risk for severe complications related to COVID-19, including ICU admission, need for mechanical ventilation, or death [21].

Emergency airway management in head and neck cancer patients presents several unique challenges as concerns for COVID-19 transmission disrupt the typical workflow of care. Ideally, all patients undergoing aerosol-generating procedures would have pre-procedure testing for COVID-19, but in emergency circumstances, this may not be possible. As such, these patients must be treated as persons under investigation (PUI) for COVID-19. Precautions taken to reduce potential exposure of healthcare providers must be balanced with the need to provide expeditious care for these critically ill patients. FFL, a mainstay of airway evaluation in head and neck patients, is considered an aerosol-generating procedure and appropriate personal protective equipment (PPE) including an N95 mask or powered air purifying respiratory (PAPR), eye protection, and gloves is recommended by the American Academy of Otolaryngology-Head and Neck Surgery [22]. Steps should be taken to reduce the number of providers exposed during the procedure, such as recording the exam or having a senior member of the team perform the exam alone. Airway support measures, such as high-flow nasal cannula or non-invasive positive pressure ventilation, are also at high risk for aerosolization of respiratory secretions and should be used with caution [23].

Awake tracheostomy is particularly high risk for transmission of COVID-19 given the high likelihood of coughing during the procedure, inability to control ventilation when entering the airway, and respiratory distress of the patient during the procedure [24]. All personnel involved in these procedures should wear full PPE including N95 masks or PAPRs. Protocols for emergency airway management during the COVID-19 pandemic are not standardized and may not be tailored specifically for the head and neck cancer population. When possible, fiberoptic intubation after application of sufficient topical anesthetic should be performed as it allows for controlled entry of the airway and the ability to hold ventilation, thus reducing the aerosolization of respiratory secretions. In patients with difficult anatomy or in emergent circumstances this algorithm may not be feasible. In these cases, the providers should proceed directly to awake tracheostomy and take all possible precautions to avoid unnecessary exposure of healthcare personnel to respiratory secretions. General recommendations from the New York Head and Neck Society regarding tracheostomy for COVID-19 patients included performing tracheostomy in a negative pressure room (e.g., in the intensive care unit or a designated pod within the operating room), preoxygenation and holding ventilation when entering the airway, avoiding monopolar cautery or harmonic technology and use of cold instrumentation, minimizing the use of suction, and potentially utilizing percutaneous tracheostomy when feasible [25]. Alternative measures such as securing a face mask with a seal around the mouth and nose rather than the standard nasal cannula may reduce aerosolization during awake tracheostomy [24].

Bleeding Management

Patients with head and neck cancer, most notably SCCHN, can develop life-threatening bleeding. There is a rich vascular supply to the head and neck region. Bleeding can occur from direct tumor involvement and/or as a side effect of therapy [26]. The most common cause of bleeding is poor wound healing after surgery or radiation. The initial management of bleeding in head and neck cancer patients is no different than the general population. The patient must first be stabilized. The ABCs (Airway, Breathing, and Circulation) of shock trauma should be addressed. Two large-bore intravenous lines should be obtained. Warmed isotonic electrolyte solutions such as lactated Ringer's solution or normal saline should be administered in a bolus fashion. Transfusion of packed red blood cells (pRBC) should be considered. When administering large amounts of pRBC, calcium supplementation should be considered as there are chelating agents of calcium in these blood products [27]. Laboratory studies including complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (aPTT), and other coagulation labs should be performed and corrected as needed to assist in hemostasis.

Acute Arterial Bleeding

Acute arterial bleeding from the mouth or neck can occur after treatment of SCCHN. Surgery can strip the vascular supply of the arterial wall. Radiation therapy can cause obliteration of the vasa vasorum, premature atherosclerosis, adventitial fibrosis, and fragmentation of tunica media elastic fibers leading to weakening of the arterial wall [28]. Patients with head and neck cancer have other factors that contribute to poor wound healing including nutritional compromise, poor tissue perfusion, soft tissue exposure to salivary enzymes, and infections [29].

Major arterial bleeding is often preceded by a sentinel bleed, usually from a pseudoaneurysm, that can be profuse but self-limited [29]. A spontaneous cessation of brisk bleeding in a patient with SCCHN can give the emergency physician a false sense of safety. Immediate diagnostic workup followed by treatment should be obtained to prevent a catastrophic bleed. CT imaging may show irregular thickening of the arterial wall of major vessels [30]. If the patient is stabilized, CT angiography (CTA) can be an effective screening tool for locating the site of hemorrhage and can also assist in

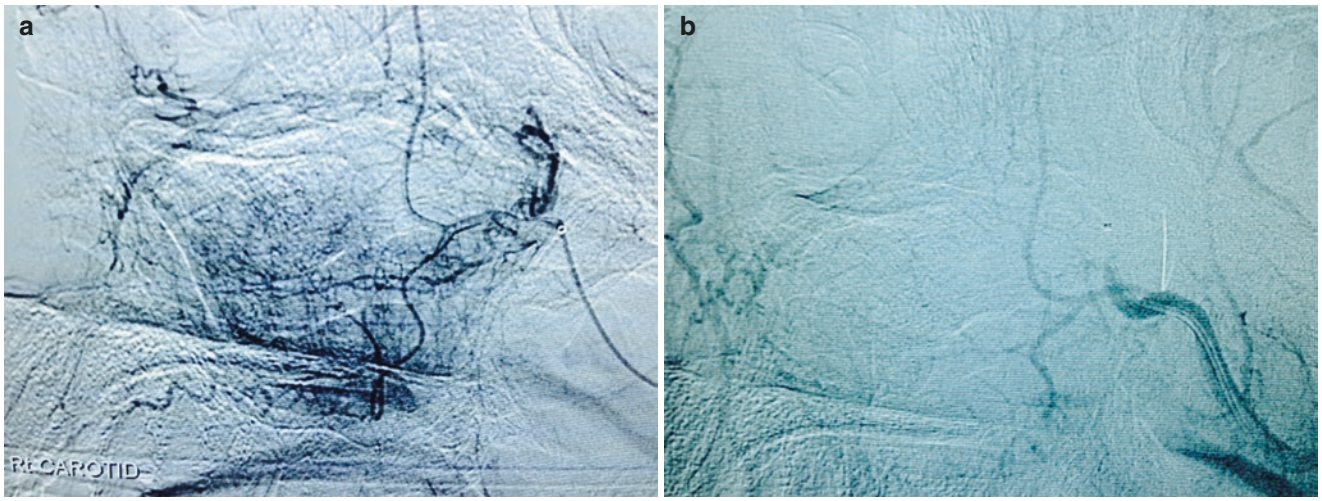

Fig. 19.6 Angiogram of the right internal maxillary artery in a patient with epistaxis from a sinonasal cancer before (**a**) and after (**b**) embolization

procedures performed by the intervention neuroradiologist [29]. Prophylactic treatment of the diseased vessel can prevent catastrophic events (Fig. 19.6).

Direct pressure is key to temporarily controlling any acute bleeding. In the head and neck, there is the additional challenge of managing the airway. If the bleeding is origination from the oral cavity or oropharynx, then the airway must be secured before effective pressure can be applied. With the airway secured, bleeding from the mouth can generally be temporized with a throat pack. If a tracheostomy tube is present, the cuff should be immediately inflated to prevent aspiration of blood into the lower airway and lungs. If the tracheostomy tube does not have a cuff, then it should be replaced with a cuffed tracheostomy tube. If a significant amount of blood becomes static in the trachea and the bronchial tree, then clots will cause total obstruction of the airway. This risk is much lower in laryngectomy patients since the oral cavity and oropharynx have no connection to the airway. Even so, it is advisable to intubate the trachea for protection in these patients during any significant bleeding episode. Once the airway is secure, the underlying cause of bleeding can be investigated and managed by a head and neck surgeon and/or interventional neuroradiologist.

Carotid Blowout

The most feared bleeding complication from SCCHN is carotid rupture (aka carotid blowout). Without immediate, aggressive intervention, carotid blowout is uniformly fatal. Before interventional angiography, hemostasis for carotid artery rupture was obtained via an open surgical approach. This was associated with 60% neurological morbidity and 40% mortality. More recently, endovascular stenting of a carotid artery rupture has shown >80% survival and far fewer neurological events. However, endovascular stent placement without further treatment has a recurrent bleeding up to 26% [29]. So, the patients who are successfully resuscitated and stented should undergo subsequent definitive surgical management (e.g., overlying soft tissue flap reconstruction) to prevent further bleeding episodes [31]. In dire cases, the ipsilateral carotid artery can be permanently occluded, albeit with at least a 15–20% risk of delayed cerebral complications [32].

Internal Jugular Vein Bleeding

Internal jugular vein bleeding, although rarer than carotid artery bleeding, can occur after treatment of SCCHN. These are typically less severe, characterized by multiple episodes, and aggravated by coughing [32]. Internal jugular vein bleeding is almost uniformly associated with a pharyngocutaneous fistula [32]. The treatment is a surgical exploration of the wound and ligation.

Tracheoinnominate Fistula

A tracheoinnominate fistula (TIF) is a connection from the trachea to the innominate artery. It is a rare complication after tracheostomy placement ranging from 0.1% to 1% in incidence and usually occurring between postoperative days 7 and 14 [31]. There are a number of factors that can predispose a tracheostomy patient to this complication including lower placed tracheotomies, over-inflated cuffs causing ero-

sion of the trachea, and anomalies of the innominate or other large caliber arteries [33]. Before this catastrophic event, there may be an ominous sign of milder pulsating bleeding from the tracheostomy (sentinel bleed) [33].

TIF has a high rate of mortality as it causes rapid exsanguination in combination with aspiration of large amounts of blood. The mortality rate approaches 100%, even when surgical intervention is taken [34]. Definitive management of a TIF requires a sternotomy and vascular repair in the operating room. Placing direct pressure against the anterior tracheal wall can temporize the bleeding. This can be done either digitally with a finger or by placing a cuffed tube, creating a temporary tamponade [33]. Endovascular embolization or placement of a stent graft of the innominate artery has also been reported [31].

Epistaxis

Epistaxis is a common reason for presentation to the ED. Management of epistaxis from head and neck malignancy or after surgery is different from ordinary epistaxis and merits special considerations. A typical case of epistaxis can usually be watched and stopped with external digital pressure and lubrication of the nasal mucosa with nasal saline spray and antibiotic ointment. Epistaxis in the setting of a sinonasal cancer can be more serious and should be handled more aggressively.

With active epistaxis, visualization with anterior rhinoscopy or endoscopy may not be possible depending on the volume of bleeding. The patient should be sitting up and positioned leaning forward to allow the bleeding to exit the nares rather than into the pharynx, where it may cause airway compromise. If the bleeding is severe, the airway may need to be secured with intubation. Packing is often required to tamponade uncontrolled epistaxis. There are dissolvable packing materials, such as cellulose polymers (Surgicel®) and porcine skin gelatin (Gelfoam®), and non-dissolvable packing materials, such as cross-linked polyvinyl alcohol (Merocel®) and balloon packs (Rapid Rhino®). A headlight, nasal speculum, and bayonet forceps should be used for placement of packing. Other products such as topical thrombin components (Floseal®) can be topically placed inside the nose to aid in hemostasis.

Given the high viral load of SARS-CoV-2 in the nasal cavity and nasopharynx, providers should proceed with caution when managing patients with known COVID-19 or unknown infection status [35]. When possible, testing for COVID-19 should be obtained prior to intervention for epistaxis. Nasal packing and other procedures to manage epistaxis are high-risk aerosol-generating procedures and appropriate PPE should be utilized, including N95 masks or PAPRs, eye protection, gown, and gloves. Noninvasive measures such as digital compression or medical management should be attempted for mild epistaxis before more invasive measures are undertaken. Absorbable packing should be considered to reduce the need for further procedures to remove packing.

Management of Treatment Complications

Surgical Complications

There are risks of complications after surgery for SCCHN beyond those already covered in this chapter (airway and bleeding). The most common complications after surgery are edema and seroma formation.

After neck dissection (cervical lymphadenectomy), it is common for patients to develop lymphedema of the lower face and neck. Patients who receive adjuvant treatment including radiation therapy and chemotherapy often have lymphedema after treatment. This most commonly presents in the neck and submental region with pitting and non-pitting edema [36]. Seroma is a collection of sterile, straw-colored serous fluid in a dead space of the surgical field and most commonly happens after neck dissection and thyroidectomy. A seroma can easily be mistaken for an abscess if the skin is red and tender. A white blood cell (WBC) may not be helpful as this can be elevated after surgery without infection. A key difference is that there are typically no clinical signs of severe infection (e.g., fever, sepsis) with seroma. If there is uncertainty, then sterile needle aspiration of the fluid can be diagnostic. Seromas typically do not require emergent treatment.

In contrast to seroma, a hematoma is a collection of blood within the surgical bed and can occur in up to 4% of all major head and neck cancer surgeries [37]. A hematoma can be distinguished from seroma by the presence of bruising and turgor of the overlying skin (Fig. 19.7). An expanding hematoma of the neck should be recognized as an emergency because of the potential for airway compression. The treatment of an expanding hematoma is evacuation of the hematoma and control of any bleeding vessels. This is best performed sterilely in the operating room to reduce the risk of infection but may be necessary at the bedside if the patient develops an unstable airway.

A chyle leak is an uncommon complication that can occur after surgery in the low neck. A chyle leak can present in a similar manner to a seroma. The defining difference is that chyle has a characteristic milky color with normal dietary intake and can have inflammatory effects. Chyle leaks present soon after major neck surgery often when drains are still in place. Most chyle leaks occur on the left due to the pres-

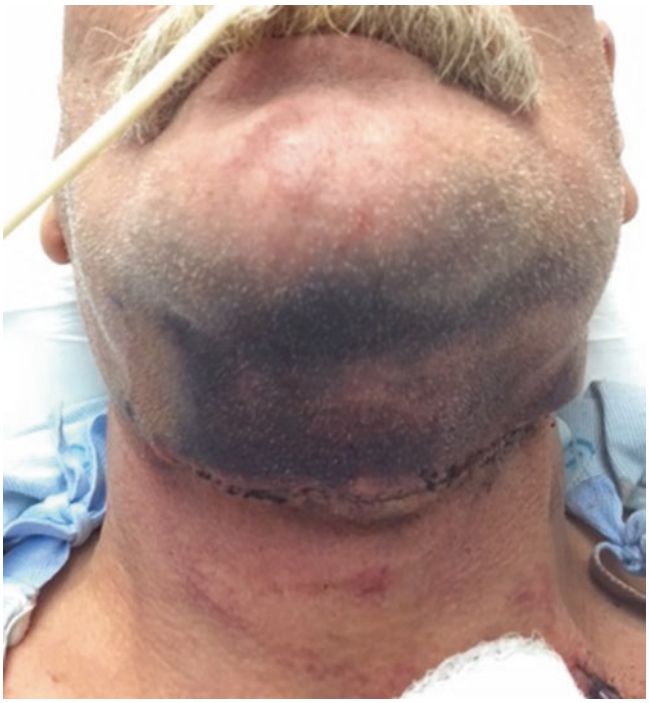

Fig. 19.7 Hematoma of the upper neck 24 h after neck dissection. Note ecchymosis of the overlying skin

ence of the thoracic duct emptying in the left subclavian vein near the internal jugular vein. Needle aspiration of a suspected chyle leak will be unproductive. Most chyle leaks can be managed conservatively with a no-fat diet and continuation of a drain.

Salivary fistula is a complication distinct to surgery of the head and neck involving the parotid gland. A salivary fistula can present like a seroma but is treated differently. There may be other signs of infection including erythema, turbid fluid in the drain, purulence, or wound breakdown. Diagnostic needle aspiration can be performed but the fluid should be tested for amylase which would be unique to saliva. Pharyngocutaneous fistula, a connection from the pharynx to the skin, can occur after major head and neck surgery, particularly in patients who have had prior treatment with radiation [38]. Treatment typically includes incision, drainage, and packing of the wound.

Radiation Therapy Complications

Radiation therapy (RT) is a commonly used method of treatment for head and neck cancer, particularly SCCHN. RT-related toxicities in the head and neck include erythema, ulceration, xerostomia, lymphedema, fibrosis, and osteoradionecrosis (ORN) of the jaw or temporal bone. RT has early and late effects on normal tissue. The early effects are caused by DNA damage and reactive oxygen species formation with resultant cell death to ciliated epithelium, blood vessels, and secretory glands [39]. The late effects are caused by ischemia from microvascular damage and fibrosis, which cause tissue edema, erythema, hemorrhage, and thickened secretions [39]. The combination of chemotherapy and radiation therapy (CRT) in the head and neck causes a synergistic effect on cancer cells but also has a more intensified impact on normal cells causing increased and more severe toxicities [40]. A large population-based study showed that 62% of head and neck cancer patients receiving CRT and 46% of patients receiving RT alone had a hospitalization or ER visit for an acute adverse effect [1]. The most prominent side effect of RT or CRT is dysphagia. Dysphagia is the result of tissue fibrosis, mucositis, laryngopharyngeal dysmotility, and xerostomia [41]. Severe dysphagia can lead to malnutrition, aspiration, and pneumonia.

A complication unique to RT of the head and neck is ORN of the jaw. ORN of the jaw is a result of direct and indirect (loss of saliva) tissue effects that culminate in poor bone healing [42]. The patient can present with recurrent or chronic pain, mandible fracture, and exposed bone in the oral cavity. ORN of the jaw after RT is often precipitated by a dental procedure. Radiation-induced necrosis of cartilage is also a well-known complication of RT. For example, radiation-induced necrosis of the larynx can occur even years after treatment [43]. Differentiating radionecrosis of the larynx from recurrent cancer can be difficult. Diagnosis is based on examination and clinical suspicion.

Chemotherapy Complications

Patients receiving chemotherapy can manifest complications in the head and neck. For primary SCCHN, chemotherapy is often used in combination with RT for definitive treatment or alone a palliative therapy. Some common agents used for SCCHN include cisplatin, carboplatin, 5-fluorouracil, docetaxel, and cetuximab. These drugs can cause nausea and vomiting, renal failure, myelosuppression, thrombocytopenia, mucositis, and neuropathy. The majority of patients treated with CRT experience severe mucositis [44]. This can lead to decreased quality of life, weight loss, gastrostomy dependence, and increased ED visits and hospitalizations [45]. When symptoms are severe enough, up to one-third of SCCHN patients will require hospitalization [46]. The most common reason for presentation to the ED during or after CRT is dehydration and malnutrition. Symptoms can be ameliorated with topical lidocaine or "magic mouthwash," which usually includes topical lidocaine, steroid, antifungal,

and antibiotic. Finally, acute hearing loss can occur from the administration of chemotherapy, most notably cisplatin. Sudden-onset tinnitus may be an early sign of acute hearing loss. Steroids and discontinuation of cisplatin may limit the loss of hearing; however, cisplatin-induced hearing loss is generally permanent.

Common Pitfalls

Neck Abscess Versus Occult SCCHN Cystic Cervical Lymph Node Metastasis

The workup of a patient presenting to the ED with a neck mass often includes a contrast-enhanced CT of the neck. It is common that the only abnormality observed is a fluid-filled collection with peripheral rim enhancement (Fig. 19.8a, b). In an adult, this almost invariably represents occult SCCHN metastatic to a cystic or necrotic lymph node in the neck. It can unfortunately be misinterpreted as an abscess, particularly if there is redness of the skin and tenderness [47]. Unlike an abscess, these patients will usually lack the cardinal findings of infection, fever, and elevated WBC. Fine needle aspiration (FNA) biopsy is the most appropriate diagnostic test of any persistent neck mass >2 cm in an adult patient. Incision and drainage are strongly discouraged without a definitive diagnosis of abscess as it can substantially alter the management of a patient with occult SCCHN metastatic to a cervical lymph node.

Sinusitis Versus Occult Sinonasal Malignancy

Acute bacterial sinusitis is a common diagnosis for patients presenting to the ED. Sinonasal malignancies, on the other hand, are very rare. However, patients with cancer involving the sinuses are often treated unsuccessfully for sinusitis for weeks or months before an alternative diagnosis is entertained. The result is a delay in diagnosis that can impact the stage of disease, treatment options, and prognosis.

There are a few key differences between patients with sinusitis and sinonasal malignancy. First, the clinical presentation is strikingly different. Patients with sinonasal cancer most often present with unilateral, rather than bilateral symptoms. Unilateral nasal obstruction, persistent nasal bleeding, facial pain or pressure, facial numbness, visual changes, and/or epiphora should be carefully evaluated for a possible sinonasal malignancy. This could most readily be accomplished with a sinus CT. Any unilateral opacification of the sinuses should prompt timely referral to an otolaryngologist (Fig. 19.9).

Ear Infection Versus Occult SCCHN of the Oropharynx

Unilateral otalgia is a common presenting symptom of SCCHN involving the oropharynx, including the tonsil or base of tongue. Other common causes of ear pain are infection and temporal mandibular joint (TMJ) disorder. It is

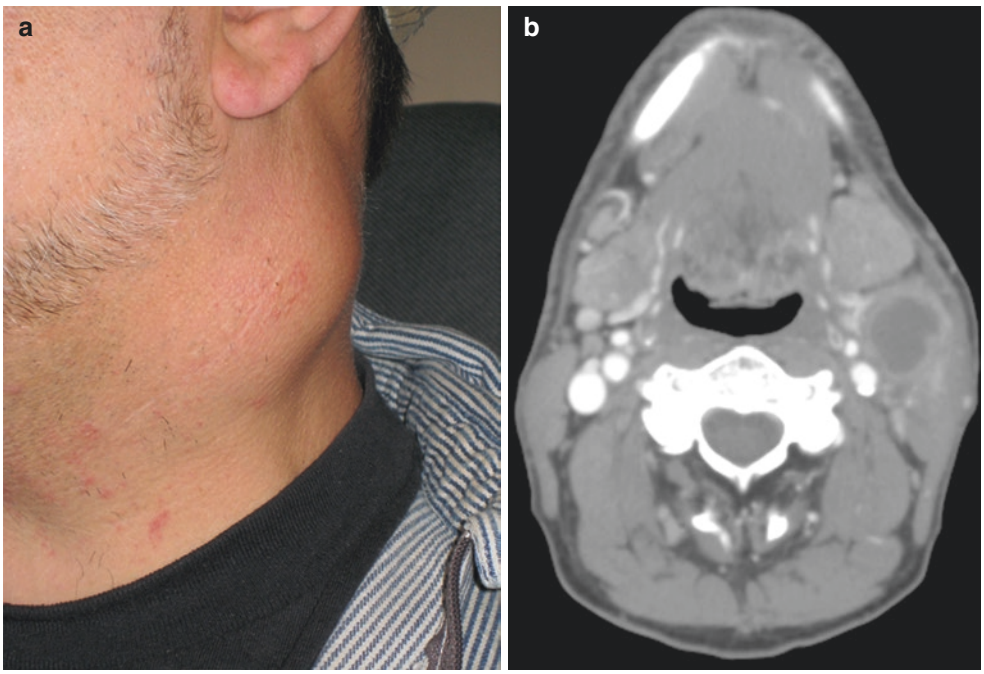

Fig. 19.8 Patient presenting with a non-tender left-sided neck mass (**a**) which appears cystic on axial computed tomography (CT) imaging (**b**). Any lateral neck mass in an adult should be considered cancer until proven otherwise, regardless of smoking status or other risk factors

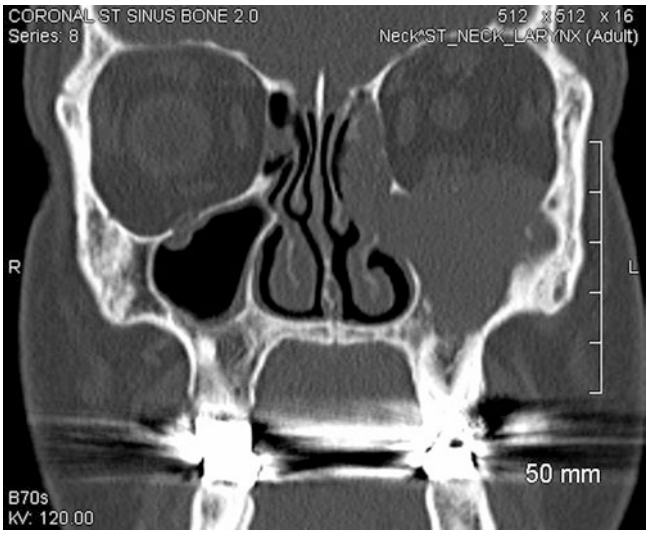

Fig. 19.9 Coronal computed tomography (CT) of the sinuses demonstrating a left-sided nasal cavity mass with opacification of the left maxillary sinus and ethmoid sinuses and invasion into the ipsilateral orbit. Any unilateral opacification of the sinuses is concerning for malignancy

important for medical practitioners in the ED to be able to distinguish between benign and malignant causes of ear pain. As with occult sinonasal malignancies, a delay in diagnosis is common for patients with SCCHN of the oropharynx.

The incidence of SCCHN involving the oropharynx (tonsil or base of tongue) continues to increase dramatically [48]. This has been attributed to the human papillomavirus (HPV) which is now associated with >70% of these cases. Patients with HPV-associated SCCHN tend to be younger and are more often non-smokers and are often not thought to be at risk of head and neck cancer [49]. However, unilateral otalgia without clinical findings of an ear infection (e.g., ear drainage, middle ear effusion, painful ear canal) should prompt a thorough evaluation of the oropharynx by a specialist to rule out occult malignancy.

Summary

The UADT is a complex area where functions of breathing and eating take place in a highly vascularized area. Patients with SCCHN frequently present to the ED with a difficult airway. Frontline physicians in the ED must have a plan for airway control in these patients. An understanding of anatomy and physiology of the surgically altered airway in patients after tracheostomy and laryngectomy, so-called neck breathers, is essential. Bleeding related to the treatment of SCCHN can be catastrophic. Therefore, control of the airway along with methods to stabilize the patient is important. The use of direct pressure to tamponade bleeding and shock trauma principles can be employed before definitive management by a head and neck surgeon. There are other treatment-related complications related to surgery, radiation therapy, and chemotherapy that must be recognized to prevent further sequelae. To avoid common pitfalls in SCCHN management, ED medical personnel must also be aware of distinctions between signs of malignancy and common otolaryngologic symptoms.

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Ophthalmic Emergencies in Cancer Patients

20

Diana Chao, Mathieu F. Bakhoum, and Bita Esmaeli

Introduction

While there are a few ophthalmological emergencies that are life-threatening, there are a number of ocular conditions in cancer patients that require immediate diagnosis and management. This chapter reviews the differential diagnosis and management of common ocular or visual symptoms encountered in a cancer hospital-based emergency department (ED). It is organized based on the symptoms that patients may present with to the ED, including acute visual loss, diplopia, red eye, proptosis, epiphora, ptosis, flashes, and floaters. A review of trauma-related ocular emergencies is outside the scope of this textbook, and the reader is referred to other texts for a detailed discussion of noncancer-related ocular emergencies [1, 2].

Acute Visual Loss

One of the most distressing ophthalmologic symptoms is the sudden loss of vision. The causes of sudden acute visual loss may be classified as those affecting the optic nerve, those affecting the retina, and those affecting the retinal vasculature.

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The primary symptoms associated with optic nerve disease may include decreased visual acuity associated with a central visual field defect, decreased color vision and contrast sensitivity, and ocular pain on eye movement. A sensitive clinical sign for the presence of asymmetric optic nerve disease is a relative afferent pupillary defect (Marcus Gunn pupil) on the affected side using the swinging-light test [3]. On ophthalmoscopy, the optic nerve head may appear swollen or pale. A red desaturation test may also be performed; when there is damage to the optic nerve, the affected eye sees the color red as a blanched orange-pink color.

Acute visual loss secondary to optic nerve disease in cancer patients can be due to a mass effect, either from a primary orbital tumor process (Fig. 20.1), secondary to an orbital metastatic process (Fig. 20.2), or from secondary extension

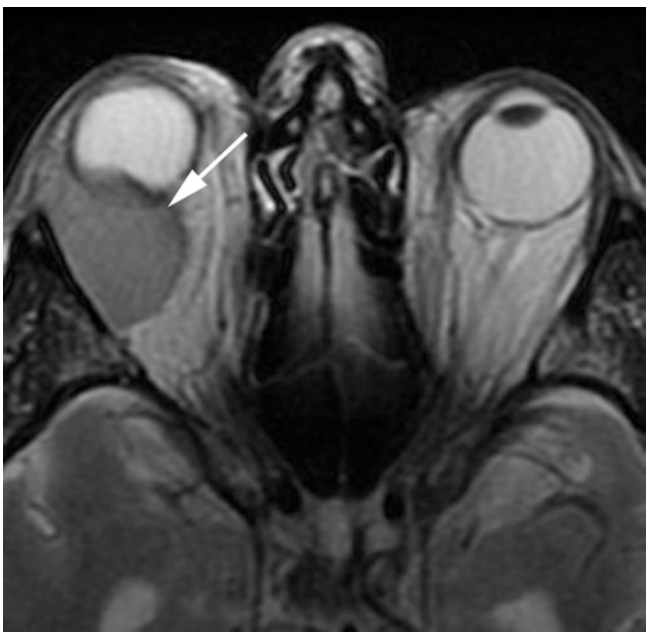

Fig. 20.1 Axial T2 image demonstrates an orbital lymphoma compressing the optic nerve and leading to visual loss. (From Debnam [73], with permission Springer Nature)

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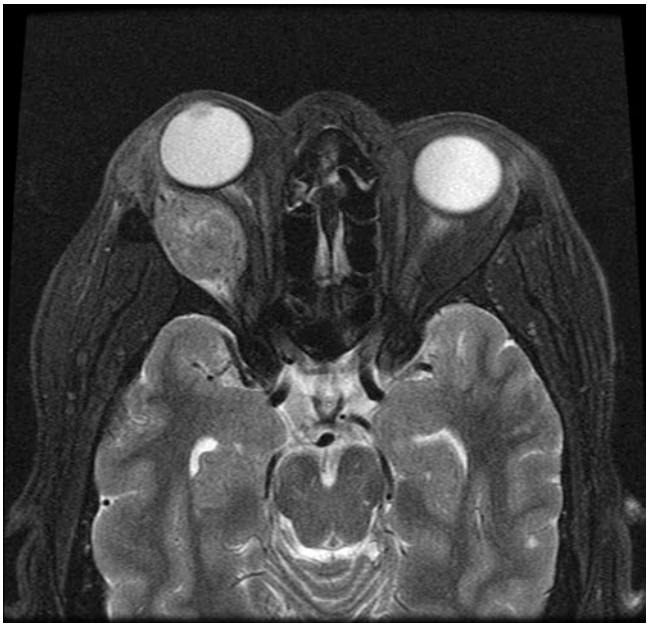

Fig. 20.2 Axial T2 image demonstrates metastasis from clear cell renal cell carcinoma to the right lateral rectus muscle. The patient presented with right eye pain, proptosis, diplopia, and blurry vision

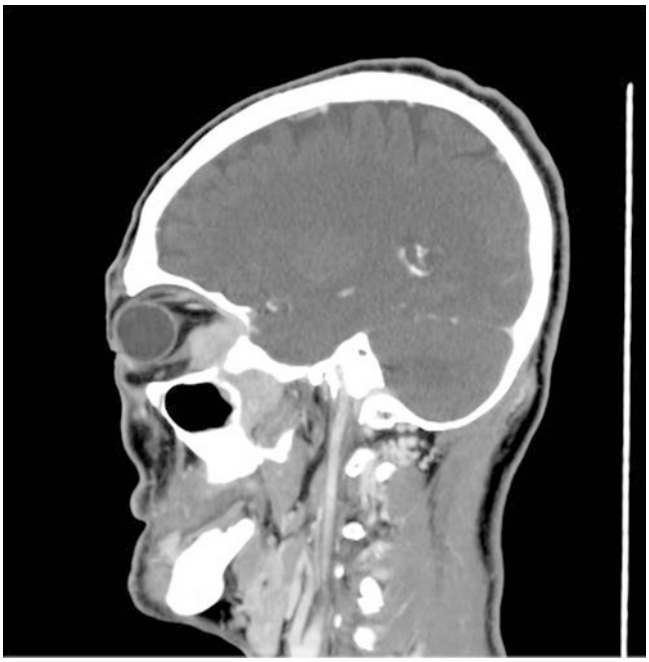

Fig. 20.3 Computed tomography sagittal plane demonstrates a nasopharyngeal carcinoma invading the orbit posteriorly through the inferior orbital fissure. (From Shinder and Esmaeli [74], with permission Springer Nature)

of tumor from paranasal sinuses (Fig. 20.3), from nasal cavity, or from the brain or skull base. Primary malignancies of the optic nerve include optic nerve glioma (Fig. 20.4), meningioma, craniopharyngioma, and medulloblastoma [4].

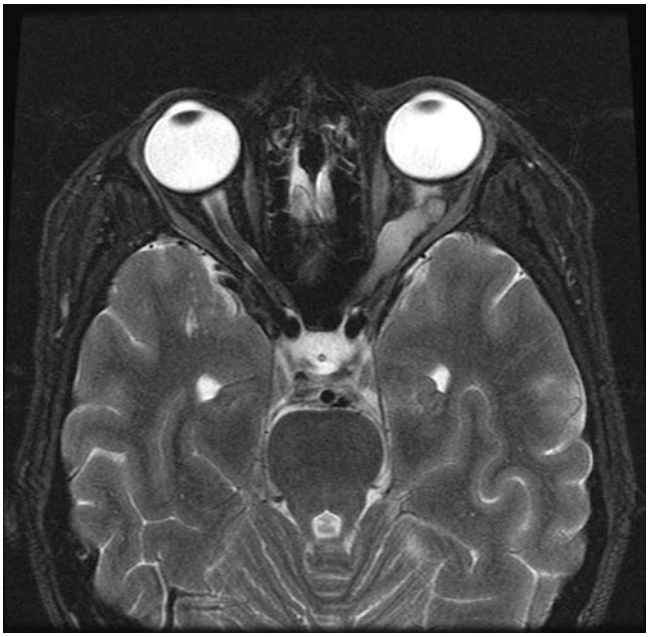

Fig. 20.4 Axial T2 image demonstrates left optic nerve glioma in a 61-year-old female who presented with visual loss in the left eye

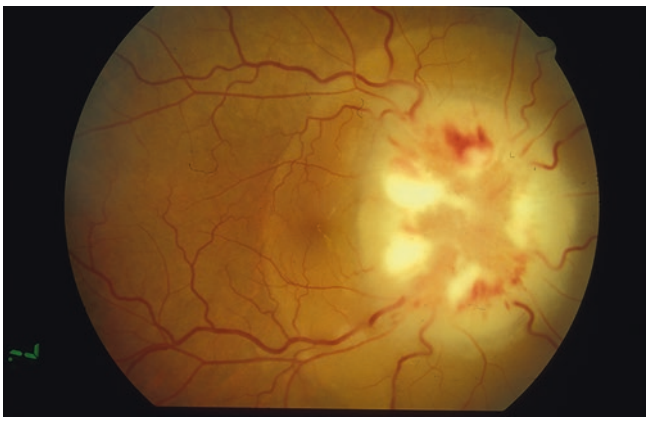

Fig. 20.5 Fundus photograph demonstrates infiltration of the optic nerve by leukemic cells, causing progressive visual loss

Infiltration of the optic nerve by leukemic or lymphomatous cells may also occur (Fig. 20.5) [5]. In addition, the optic nerve may be infiltrated by leptomeningeal disease from solid or liquid tumors. Invasive aspergillosis of the paranasal sinuses and/or orbit should also be considered in immunocompromised patients, as it is most prevalent among leukemic patients with granulocytopenia and is associated with a high mortality rate [6]. Optic nerve toxicity secondary to chemotherapeutic agents is another possible cause of optic neuropathy in cancer patients.

The most common noncancer-related cause of optic neuritis (optic nerve swelling) is multiple sclerosis; however, optic neuritis may also result from inflammatory conditions,

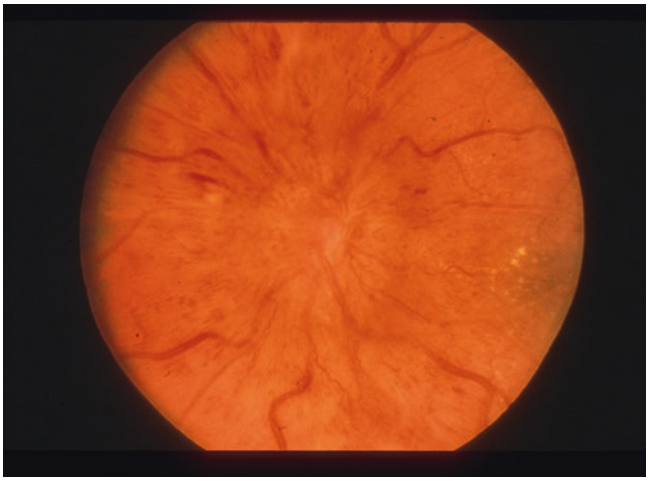

Fig. 20.6 Fundus photograph demonstrates ischemic optic neuropathy in a patient with diabetes mellitus who experienced acute painless loss of vision

such as Wegener's granulomatosis (granulomatosis with polyangiitis), systemic lupus erythematosus, and sarcoidosis, or it may be idiopathic. Infectious etiologies (including syphilis and Lyme disease) may also produce similar findings. In the elderly population or in patients with atherosclerosis, hypertension, and/or diabetes, the most common cause of acute visual loss of optic nerve origin is an ischemic optic neuropathy (Fig. 20.6). In the older population, giant cell arteritis is an important form of ischemic optic neuropathy that is sometimes associated with polymyalgia rheumatica [7]. Giant cell arteritis requires prompt diagnosis and treatment with high-dose systemic steroids to prevent progressive and sometimes bilateral visual loss. In diabetic patients or in the immunocompromised cancer patients, the possibility of orbital cellulitis or fungal infections such as mucormycosis or aspergillosis of the sinus with extension into the orbit should also be considered as a cause of optic nerve swelling and compression.

The preferred diagnostic test to evaluate optic nerve disease is magnetic resonance imaging (MRI) of the brain and orbit, with and without gadolinium, fat suppressed. MRI can usually demonstrate the extent of optic nerve disease, although may be normal in the early stages of leptomeningeal disease [8].

The management of optic nerve disease depends on the etiology. In cancer patients, the initial management may include systemic antibiotics or antifungals, chemotherapy, external beam radiation therapy, high-dose steroids, or surgery [9–11].

Retinal disease (particularly if it involves the macula, where visual acuity is most sensitive) may cause acute visual loss. Symptoms associated with retinal disease include decreased vision, metamorphopsia, flashes of light, new floaters, and a "curtain" over the visual field. A dilated fundus examination is necessary to correctly diagnose the retinal causes of acute visual loss.

Rhegmatogenous retinal detachment is the most common type of detachment, and it occurs when there is a tear or break in the retina, allowing fluid to accumulate in the subretinal space, separating the neurosensory retina from the underlying retinal pigment epithelium. In cancer patients, serous and exudative retinal detachments may result from leukemic or lymphomatous infiltration of the choroid and/or subretinal space, choroidal metastatic lesions (Fig. 20.7), or, less commonly, primary intraocular tumors such as uveal melanoma. Serous and exudative detachments occur despite the absence of a hole, tear, or break. Opportunistic infections such as those with *Cytomegalovirus* (CMV) (Fig. 20.8), herpes simplex virus (HSV), herpes zoster virus (HZV), and *Candida* may cause retinitis in immunocompromised patients. Retinitis due to HSV or HZV may cause rapid

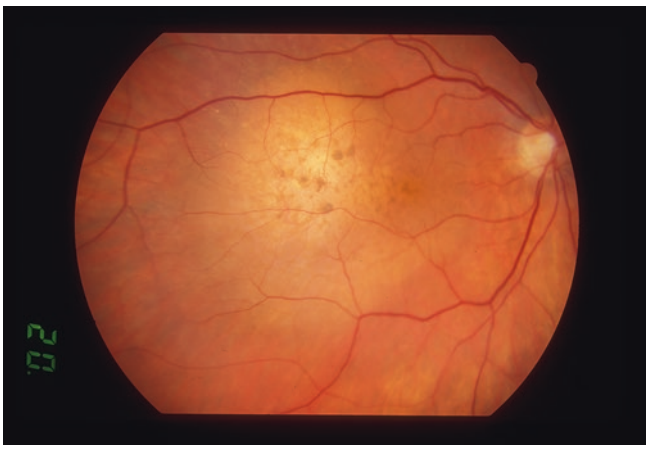

Fig. 20.7 Fundus photograph demonstrates a choroidal metastatic lesion causing elevation of the choroid and metamorphopsia

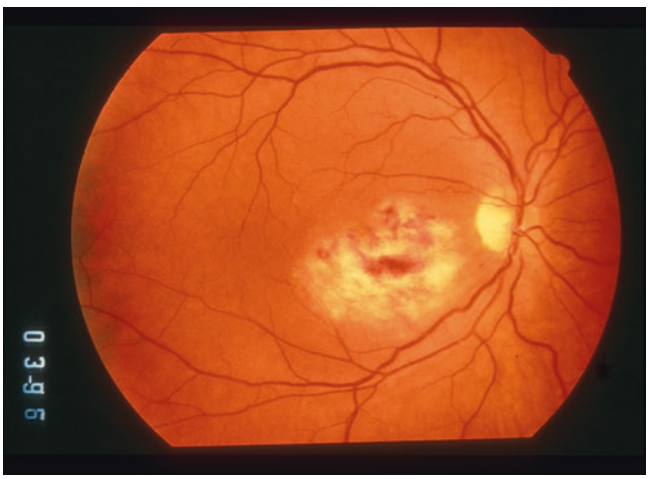

Fig. 20.8 Fundus photograph demonstrates CMV retinitis, characterized by necrosis and hemorrhage often in the posterior pole

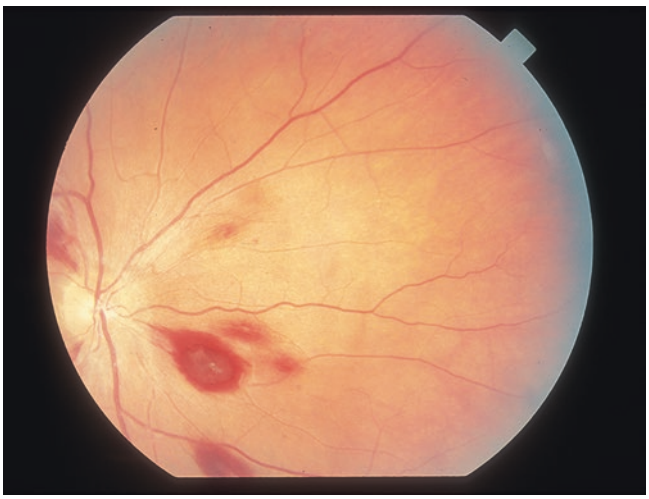

Fig. 20.9 Fundus photograph demonstrates spontaneous retinal hemorrhage in a patient with acute myeloid leukemia and thrombocytopenia

visual loss to "no light perception" within 24 h [12]. It is important to diagnose the infectious forms of retinitis in a timely fashion so that the appropriate systemic therapy can be initiated as soon as possible.

Another very common cause of visual loss among cancer patients is retinal hemorrhage secondary to thrombocytopenia (Fig. 20.9) [13]. Prompt referral to an ophthalmologist is necessary for appropriate diagnosis and management. Treatment for rhegmatogenous detachments includes urgent laser photocoagulation or surgical management. For all other etiologies, timely treatment of underlying disease including chemotherapy and/or radiation for metastatic lesions and intravenous and/or intravitreal antiviral and antifungal therapy for opportunistic viral infections is necessary.

Obstruction of the retinal vasculature can also cause acute visual loss. Retinal vascular obstruction usually results from thrombi or emboli and is more likely to occur in patients with hypertension, atherosclerosis, or diabetes. However, cancer patients have the added risk of neoplasm-associated hypercoagulability [14]. Central retinal artery occlusion (CRAO) or central retinal vein occlusion (CRVO) may lead to devastating visual loss. Involvement of the smaller vessels may lead to partial visual acuity or visual field loss. Most occlusive vascular events are not reversible although they require prompt diagnosis and follow-up to address the underlying medical problems and to prevent future ocular complications from ischemic retinopathy. The visual prognosis depends on the extent of retinal ischemia. Particularly, the ischemic variety of CRVO can be complicated by secondary neovascular glaucoma and may require panretinal photocoagulation and intravitreal anti-VEGF inhibitors [15]. Prompt referral to an ophthalmologist is recommended when a retinal vascular event is suspected.

Diplopia

Diplopia (double vision) is a common symptom in cancer patients. The first thing to establish is whether diplopia is monocular or binocular and whether it is horizontal or vertical. In addition, true diplopia must be distinguished from blurred vision, in which the image is blurred, but is not in fact double. If diplopia persists after one eye is covered, the patient has monocular diplopia, which is almost certainly not a neurologic problem. The usual causes of monocular diplopia include refractive error or media opacity (i.e., cataract). In contrast, if diplopia is present only when both eyes are open, it is binocular in nature, and there is usually an underlying neurologic or extraocular motility problem. Binocular diplopia can be horizontal, vertical, or torsional [16]. Extraocular motility exam should be performed to assess whether only one or multiple cranial nerves are affected and for any signs of ptosis.

Specific neurologic causes of binocular diplopia include cranial nerve III, IV, or VI palsies, or a mechanical process that may limit the function of the extraocular muscles. If only one cranial nerve or extraocular muscle is affected, then a simple noncomitant diplopia may develop. In contrast, leptomeningeal disease or any space-occupying lesion in the orbital apex, superior orbital fissure, or the cavernous sinus may affect multiple cranial nerves at the same time, resulting in a more complex pattern of diplopia.

While cranial nerve palsies can be secondary to an ischemic event (particularly in patients with hypertension, diabetes, or atherosclerosis), in cancer patients, the most common etiology is tumor extension in the orbital apex or cavernous sinus. Extraocular muscles may also be compressed or entrapped by a mass, or they may be infiltrated by inflammatory or neoplastic processes. Opportunistic infections, particularly fungal infections secondary to mucormycosis or aspergillosis, may extend into the orbit from the paranasal sinuses. A high index of suspicion for fungal cellulitis or pansinusitis is necessary to make the correct diagnosis and initiate therapy for these potentially fatal infections in immunocompromised patients [17].

Another important but less common cause of third cranial nerve palsy, particularly if pupillary fibers are involved, is a cerebral aneurysm. This is not unique to cancer patients but should be considered on the differential diagnosis of a patient with an acute onset of third cranial nerve palsy.

In the emergency evaluation of a patient with an acute onset of diplopia, an imaging study (ideally, an MRI of the brain and orbit with and without gadolinium, fat suppressed) is often necessary to rule out or establish the diagnosis and extent of orbital or cavernous sinus involvement if any.

If a cerebral aneurysm is suspected, magnetic resonance angiogram (MRA) or computed tomography angiography (CTA) of the brain is indicated.

The treatment of diplopia depends on the underlying cause and (usually in cancer patients) entails treatment of the underlying tumor or infectious etiology. The patching of one eye or temporary Fresnel prisms may help the patient symptomatically until the exact cause and treatment for diplopia is determined.

Red Eye

There are many possible causes of a red eye in cancer patients. It is helpful to classify the causes of a red eye on the basis of intraocular structures that may be the cause of inflammation on the surface of the globe. Any disease process that can cause inflammation in the conjunctiva, cornea, iris, anterior chamber, ciliary body, or sclera can present as a red eye. Therefore, it is important to perform a comprehensive ophthalmologic examination to identify the correct cause.

Conjunctivitis is probably the most common cause of a red eye. Conjunctivitis can be due to infectious etiology such as bacteria (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Chlamydia*, *Neisseria gonococcus*) or viruses (adenovirus, herpes simplex virus [HSV]) [18]. However, occasionally, the cause is not infectious. The inflammatory causes of conjunctivitis include toxic conjunctivitis secondary to the excessive or inappropriate use of topical antibiotics (medicamentosa), allergic conjunctivitis, and acute or chronic ocular graft-versus-host disease.

Subconjunctival hemorrhage and hemorrhagic chemosis are benign conditions that may cause asymptomatic, sudden, painless red eye (Fig. 20.10). Conservative management with lubrication of the eye and observation for spontaneous resolution over several weeks is appropriate.

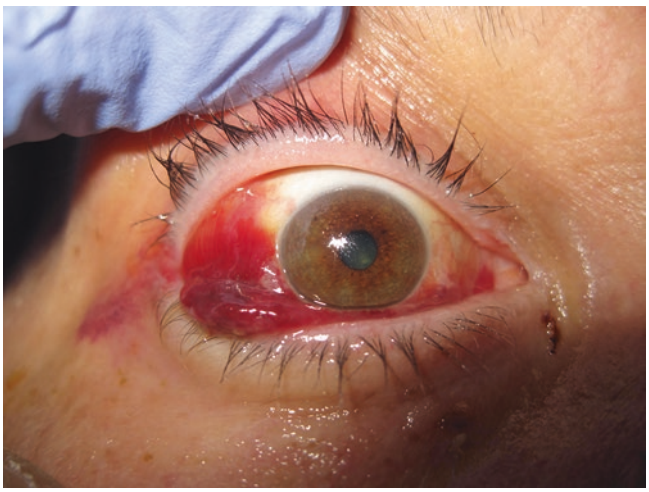

Fig. 20.10 Subconjunctival hemorrhage, causing painless red eye, in a 57-year-old patient who has a history of acute lymphoblastic leukemia and low platelet count (30,000/μL)

Superficial keratopathy secondary to ocular graft-versus-host disease (GVHD) or as a side effect of cancer chemotherapeutic agents such as arabinosylcytosine (ara-C) can cause ocular surface irritation, corneal epithelial defects, and, possibly, a red eye [19, 20]. Many other chemotherapeutic agents such as docetaxel and 5-fluorouracil are secreted in the tear film and may lead to conjunctivitis. Slit-lamp examination of the cornea using topical fluorescein dye and cobalt-blue light to assess for decreased tear film, punctate epithelial erosions, pseudomembranes, serosanguinous exudates, and corneal epithelial defects is performed to evaluate for most forms of superficial keratopathy. The management of conjunctival or corneal problems secondary to ocular GVHD entails the use of topical lubricants, cyclosporine drops, punctal plugs, and topical and/or systemic administration of immunosuppressive agents, such as steroids and tacrolimus [21]. Superficial keratopathy secondary to ara-C use is treated with topical steroids, lubricating artificial tears, and ophthalmic ointment, and in refractory cases by lowering the dose of ara-C.

Another common cause of superficial keratopathy in cancer patients is exposure keratopathy secondary to facial palsy. Facial paralysis secondary to the compressive effects of a parotid mass or due to ablative surgery for malignancies in the parotid area can result in inadequate eyelid closure and chronic corneal exposure [22]. The immediate treatment of exposure keratopathy entails the use of lubricating artificial tears and ophthalmic ointments. If facial paralysis is expected to last longer than a few weeks, periocular surgery, such as placement of a gold weight in the upper eyelid, repair of paralytic lower eyelid, and a lateral tarsorrhaphy, should be considered [23].

Infectious keratitis is another important cause of red eye and can be caused by bacterial (*S. aureus*, *S. pneumoniae*, *N. gonococcus*, *Moraxella*, *P. aeruginosa*), viral (adenovirus, HSV, HZV), or fungal (*Candida*, *Aspergillus*) organisms [24]. Herpes zoster ophthalmicus occurs when varicella-zoster virus is reactivated in the ophthalmic (V1) division of the trigeminal nerve and is associated with immunosuppression, and it may be a harbinger of increased risk of cancer [25] or other immunocompromised states. It may present with periorbital vesicle formation in a unilateral, V1 dermatomal distribution with associated red eye and pseudodendritic fluorescein-staining pattern under cobalt light. Prompt diagnosis and treatment of HZV with systemic antiviral agents like acyclovir and topical agents is appropriate. The diagnosis and management of infectious keratitis requires the direct involvement of an ophthalmologist. Management often involves obtaining corneal cultures and instituting topical fortified antibacterial, antiviral, or antifungal agents.

Acute angle-closure glaucoma may also cause a painful red eye. It occurs in patients who have narrow angles that become blocked by the iris. Symptoms and signs of acute angle-closure glaucoma are pain, redness, blurred, or "steamy" vision from corneal edema, halos around lights, and a mid-dilated pupil. The intraocular pressure can rise to 50–60 mmHg, and urgent medical treatment to lower the pressure is necessary to avoid permanent vision loss. There are many causes of acute angle-closure glaucoma, and prompt diagnosis is necessary for appropriate treatment. Anticholinergic or sympathomimetic medications dilate the iris and lead to crowding of the anterior chamber angle peripherally [26]. A mass in the ciliary body or choroid can also push the iris forward and cause angle closure [27]. Primary intraocular tumors such as uveal melanomas or medulloepitheliomas may be present in the angle and may obstruct the aqueous outflow. The medical management of angle-closure glaucoma in the ED includes the immediate use of topical antiglaucoma medications, and systemic carbonic anhydrase inhibitors are often necessary to bring the intraocular pressure down to a safe level. For primary acute angle-closure glaucoma, the patient should be referred to an ophthalmologist for consideration of a laser peripheral iridotomy after the intraocular pressure has been brought down to a safer level with medications [28].

Inflammation of the iris, ciliary body, or choroid is referred to as uveitis. In addition to red eye, uveitis can present with pain, photophobia, blurred vision, and miosis. Anterior chamber cells and flare noted during slit-lamp biomicroscopy are the hallmarks of iritis or uveitis. Uveitis is thought to be idiopathic in about 50% of cases or can be associated with various autoimmune processes such as rheumatoid arthritis, lupus, ankylosing spondylitis, and Wegener's granulomatosis (granulomatous polyangiitis) [29]. In immunocompromised patients, infectious causes of uveitis must be considered. The most severe form of intraocular infection, endogenous endophthalmitis, can initially present as mild but progressively worsening uveitis [30]. Once the diagnosis of endogenous endophthalmitis is suspected, blood culture and vitreous biopsy are often necessary to identify the causative infectious organism. Prompt referral to an ophthalmologist is necessary for diagnosis and management. Treatment for uveitis due to noninfectious causes includes the judicious use of topical steroids and cycloplegic drops to decrease the inflammation in the anterior chamber and prevent ciliary body spasm. For suspected endogenous endophthalmitis, broad-spectrum intravenous antimicrobial therapy is administered until sensitivity results are available from the vitreous biopsy cultures. Intravitreal injection of antibiotics or antifungal drugs is the treatment for endogenous endophthalmitis, and in some cases, a surgical vitrectomy may be necessary both for diagnostic and for therapeutic purposes [31, 32].

Epiphora

True epiphora (excessive tearing) results from an obstruction of the tear drainage apparatus. Epiphora must be differentiated from pseudoepiphora, which may be caused by ocular surface irritation due to conditions such as dry eye syndrome, ocular graft-versus-host disease, and exposure keratopathy. The most common cause of epiphora in the general population is primary nasolacrimal duct blockage which is due to obstruction of the nasolacrimal duct at its junction with the lacrimal sac [33]. Primary idiopathic nasolacrimal duct blockage occurs more frequently in women and is involutional in nature. In cancer patients, however, the most common etiology for epiphora is likely to be (a) mechanical blockage of the tear drainage pathway secondary to either primary lacrimal sac or nasolacrimal duct cancers or from extension of tumors from the paranasal sinus or nasal cavity [34], (b) canalicular and nasolacrimal duct stenosis secondary to chemotherapy [35, 36], or (c) canalicular or nasolacrimal duct obstruction secondary to radiation therapy [37, 38]. Common chemotherapeutic agents that are known to cause canalicular stenosis include S-1, 5-fluorouracil, mitomycin C, and docetaxel (Taxotere) [39–42]. Nasolacrimal duct obstruction may also occur secondary to local toxicity or active uptake of radioactive iodine used in the treatment of thyroid carcinoma [43–45]. Because timely diagnosis of early canalicular stenosis in patients receiving these agents can lead to early insertion of silicone tubing in the nasolacrimal duct and therefore prevention of further narrowing of the canaliculi, appropriate referral to an ophthalmologist early in the course of therapy with these agents is crucial.

Acute dacryocystitis is another important cause of epiphora. The infectious causes for acute or chronic dacryocystitis include *S. aureus*, *S. pneumoniae*, and *Haemophilus influenzae* [46]. Clinical signs associated with dacryocystitis are epiphora, mucopurulent discharge upon pressure over the lacrimal sac, and erythema and edema over the lacrimal sac. Initial treatment for infectious dacryocystitis involves systemic antibiotics and warm compresses. A dacryocystorhinostomy may be necessary to prevent future episodes of dacryocystitis, particularly in immunocompromised patients [47].

Proptosis

Proptosis (outward protrusion of the eye) may be caused by an orbital mass or a diffuse inflammatory or infiltrative process involving the retrobulbar space. Other possible associated symptoms and signs may include diplopia, decreased vision, and multiple cranial neuropathies secondary to involvement of the orbital apex.

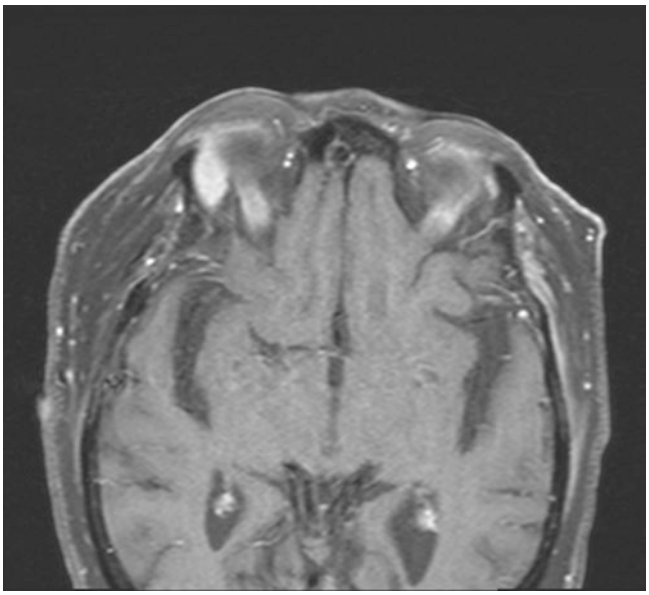

Fig. 20.11 Axial T1 image demonstrates a right lacrimal gland lymphoma in a 75-year-old female who presented with a slow-growing painless mass and mild proptosis

The most common primary cancer affecting the orbit in adults is lymphoma (Fig. 20.11) [48, 49]. Orbital lymphoma can be the extranodal manifestation of systemic lymphoma or may be the only site of lymphomatous involvement [50, 51]. Other benign or malignant tumors that can cause proptosis include optic nerve glioma, meningioma, orbital hemangioma, sarcoma, and metastatic lesions [52]. The most important cause of sudden and progressive proptosis in children is orbital rhabdomyosarcoma [53]. Another important cause of proptosis, particularly if associated with pain and inflammatory signs, is orbital pseudotumor. The diagnosis of orbital inflammatory syndrome (orbital pseudotumor) is a diagnosis of exclusion and should be made only after an orbital biopsy specimen proves to be negative for malignancy [54]. Timely diagnosis with diagnostic imaging (preferably MRI of the brain and orbit with and without gadolinium, fat suppressed) and orbital biopsy is important for institution of appropriate therapy. Management of proptosis consists of treatment of the underlying cause. It is important to avoid the administration of systemic steroids until the diagnosis is clearly established, ideally on the basis of an orbital biopsy in addition to MRI to rule out lymphoma, orbital metastasis, or rhabdomyosarcoma as the underlying cause of proptosis. The use of anti-inflammatory agents can mask the clinical signs and symptoms, delay diagnosis, and lead to a lower yield for an orbital biopsy. Prompt referral to an orbital and oculoplastic surgeon is appropriate when a patient presents with acute proptosis. An experienced orbital specialist may be able to recognize common radiographic features of common orbital lesions and sometime avoid a biopsy, but in most instances, if radiographic features are not classic for a benign vascular lesion such as hemangioma, the most appropriate next step after an imaging study is an orbital biopsy or complete excision of the mass depending on the radiographic features.

Orbital cellulitis may also present as proptosis, and it is associated with visual loss, decreased and painful extraocular movements, and general orbital congestion. Orbital cellulitis usually results from the direct extension of infection from the paranasal sinuses, especially the ethmoidal sinus [55]. However, direct inoculation from trauma, extension of an eyelid infection, and septicemia may also cause orbital cellulitis [56]. The causative infectious organisms are typically *S. aureus*, *H. influenzae*, *S. pneumoniae*, or fungi, such as *Aspergillus* [57]. Orbital cellulitis may be complicated by the formation of an orbital abscess or by direct extension of infection into the cavernous sinus and the brain, a complication with a high risk of mortality [58]. Immediate treatment with systemic antibiotics and antifungals is prudent when orbital cellulitis or an orbital abscess is suspected. An orbital abscess can be diagnosed by computed tomography (CT) or MRI and usually requires immediate surgical drainage, particularly if it is associated with progressive visual loss or proptosis [59].

Proptosis can also be caused by orbital hemorrhage. Possible causes include postoperative hemorrhage, trauma, and hematologic disorders [60]. The patient's vision and intraocular pressure (IOP) should be immediately assessed because retrobulbar hemorrhage may cause a compressive optic neuropathy that may lead to permanent visual loss. If the vision is decreased or the IOP is elevated above 30–35 mmHg, a lateral canthotomy and cantholysis should be considered in the ED to expand the orbital volume and relieve orbital pressure [61]. In the pancytopenic cancer patients who are often pancytopenic due to chemotherapy, more conservative measures such as the use of pressure-lowering glaucoma drops may be more appropriate and should be tried first as a canthotomy may lead to continuous oozing and bleeding from the orbit. Orbital emphysema can rarely yield findings similar to those of orbital hemorrhage, and a lateral canthotomy and cantholysis or needle decompression may also be indicated if symptoms and signs of compartment syndrome of the orbit occur [62, 63]. The usual cause of orbital emphysema is trauma or a history of tracheal or thoracic surgery [64].

Ptosis

Ptosis (droopiness of the upper eyelid) can be gradual or sudden in onset. As with other symptoms discussed in this chapter, determining the underlying cause is the most important

aspect of the management of ptosis in the ED. The most common cause of ptosis in adults in the general population is involutional ptosis. In children, a congenital abnormality of the levator muscle is the most common cause of ptosis. In cancer patients, the most common cause of ptosis is neurologic. A palsy of the third cranial nerve due to primary or metastatic tumors of the base of the skull can cause ptosis, decreased extraocular muscle movement, and a dilated pupil. Perineural invasion secondary to cutaneous carcinomas of the facial skin can also cause multiple cranial neuropathies, including a third nerve palsy [65].

Another neurologic cause of ptosis is Horner syndrome. Horner syndrome refers to the triad of ipsilateral mild ptosis (≤2 mm), miosis of the pupil, and anhidrosis [66]. A mass effect anywhere along the path of sympathetic fibers can cause Horner syndrome. This three-neuron chain originates in the hypothalamus. The second-order neurons originate in Budge's center (C8–T2) and wind over the lung apex. The third-order neurons originate in the superior cervical ganglion, where they follow the carotid artery and then the fifth and sixth cranial nerves before they accompany the third cranial nerve to the eye. When ipsilateral miosis is associated with ptosis, Horner syndrome must be ruled out. Associated signs and symptoms may be helpful in determining the location of the lesion causing Horner syndrome. For example, ataxia, nystagmus, and weakness may indicate a first-order Horner syndrome from a brain tumor, whereas coughing, hemoptysis, or shoulder pain may indicate a lung process (the so-called Pancoast tumor) and thus a second-order Horner syndrome. Other common causes of Horner syndrome among cancer patients are iatrogenic causes, such as surgery or radiation in the cervical and neck area. Heterochromia in children usually indicates congenital Horner syndrome and does not require extensive work-up or treatment. Pharmacologic testing with cocaine or apraclonidine may result in reversal of anisocoria in patients with Horner syndrome and can help in confirming the diagnosis; hydroxyamphetamine drops may also help localize the lesion [67].

Another cause of ptosis may be mechanical. For example, inflammatory changes in the upper eyelid due to orbital or paranasal sinus infection, surgical trauma, or external beam radiation therapy may cause temporary ptosis. An isolated tumor in the upper eyelid, such as a lacrimal gland carcinoma or lymphoma, plexiform neurofibroma, or any other tumor that extends to the superior orbit, may also lead to mechanical ptosis of the upper eyelid.

Flashes and Floaters

Flashes of light, "showers of new floaters," and a "curtain" coming down over the visual field can be ominous symptoms of vitreoretinal traction, possible retinal tear, or retinal detachment (please refer to "acute vision loss" section mentioned earlier in the chapter). A thorough dilated funduscopic examination by an ophthalmologist is necessary to determine the exact nature of vitreoretinal pathology and to rule out retinal tears or retinal detachment in patients who complain of an acute onset of flashes and floaters, particularly if these symptoms are associated with a loss of vision.

Vitritis (inflammation of the vitreous gel) can be caused by intraocular neoplasms, most commonly leukemia and lymphoma, and it can present with the onset of floaters and gradual loss of vision [68]. In patients whom intraocular leukemia or lymphoma is suspected, a MRI of the brain/orbit with and without contrast is necessary to evaluate for central nervous system (CNS) involvement as the CNS is frequently involved [69]. A vitrectomy and vitreal biopsy may be required to make a definitive diagnosis [70].

A common benign condition that can also cause the acute onset of flashes and floaters is acute posterior vitreous detachment, which is mostly secondary to senescence or trauma [71, 72]. Various forms of retinitis, endogenous endophthalmitis, and posterior uveitis may also present with the same initial symptoms. Management of endophthalmitis includes blood cultures, possible vitreous biopsy to determine the causative organism, and immediate intravenous antibiotics.

Conclusion

Ophthalmological emergencies in cancer patients are multifaceted. In most instances, consultation with an ophthalmologist is necessary to insure the timely diagnosis and management of these conditions. A general understanding of the different components of an eye examination and the differential diagnosis for common ocular presentations may help the oncologist or emergency physician with triaging, work-up, and initial treatment of these conditions until the patient can be examined by an ophthalmologist.

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Cardiovascular Oncologic Emergencies

21

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Introduction

Cancer and its treatment are associated with an enormous burden for patients [1]. Cancer itself may be life-threatening, and cancer therapies are often associated with cardiovascular toxicities (Fig. 21.1) [2]. An overview of various cardiovascular toxicities will be presented, including ischemic manifestations, non-ischemic vascular conditions, pericardial diseases, cardiomyopathies, myocarditis, conduction disturbances, and valvular heart disease. We will also address the utility of imaging modalities and strategies in the prevention, diagnosis, and management of many of these emergent cardiovascular oncologic toxicities. Finally, we end the chapter with brief comments on cardio-oncologic in the COVID-19 era.

Ischemic Cardiovascular Manifestations

Case Study

A 63-year-old postmenopausal female with a past medical history of untreated hyperlipidemia and obesity was diagnosed with invasive ductal carcinoma following screening mammogram. Approximately 18 months prior to this diagnosis, she presented with substernal chest pain and a computed

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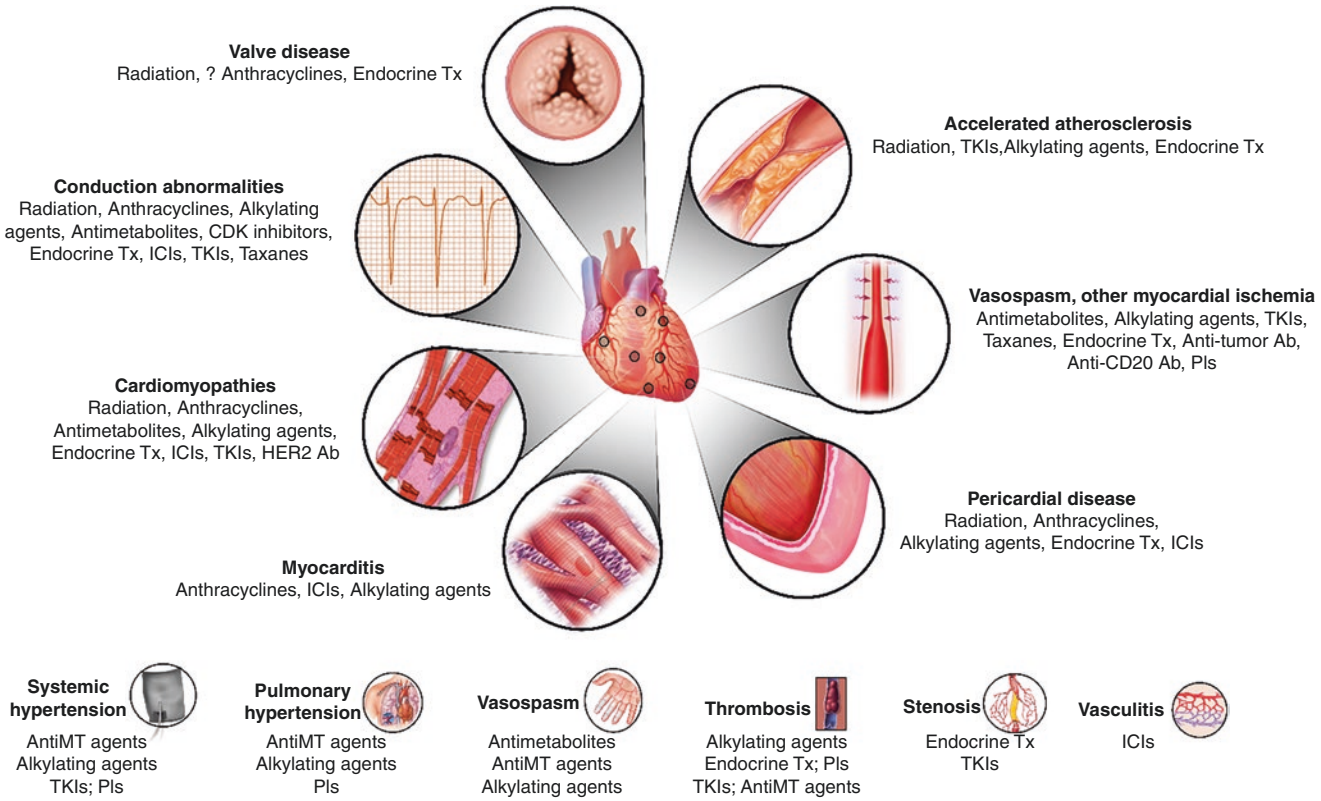

Fig. 21.1 Cardiovascular toxicities of various cancer therapies. (From Brown [2], Creative Commons Attribution License [CC BY])

tomography angiography (CTA) revealed proximal left anterior descending (LAD) coronary artery disease without flow-limiting stenosis, calcification, and possible flow-limiting stenosis within a diminutive diagonal branch with a calcium score of 45 and a Coronary Artery Disease-Reporting and Data System (CAD-RAS) score of 3. Initiation of aspirin and statin therapy were discussed at length; however, the patient declined. She underwent right breast mastectomy with pathology consistent with low-risk stage 1A ER+ HER2- RS2 oncotype. Per her primary oncologist, a plan was made to initiate aromatase inhibitor (AI) therapy without additional chemotherapy; however, initiation was delayed due to infection of the breast expander after reconstructive surgery.

On post-op day 1 of removal of the infected breast expander, and now 2 months from initial cancer diagnosis, the patient experienced sudden-onset chest pain and shortness of breath at home. EMS arrived within 30 minutes and administered 325 mg aspirin. En route, she went into ventricular fibrillation requiring cardiopulmonary resuscitation for approximately 1 minute and one dose of epinephrine after which return of spontaneous circulation was achieved. On arrival to the emergency department, she was hemodynamically stable, but in mild respiratory distress. Electrocardiogram demonstrated acute ST segment elevations in the anterior leads (Fig. 21.2)*. Bilevel positive airway pressure was started promptly, as well as a nitroglycerin infusion and administration of intravenous furosemide 80 mg. She was given 180 mg ticagrelor and taken emergently for cardiac catheterization.*

Coronary angiography revealed 100% occluded proximal LAD without other significant coronary artery disease. Percutaneous coronary intervention (PCI) of the LAD was performed, and drug-eluting stent was deployed resulting in TIMI 3 flow. Transthoracic echocardiogram showed diffuse apical and mid septal left ventricular segment akinesis with mild reduction in ejection fraction of 40–45%. She was continued on dual antiplatelet therapy (DAPT) with aspirin and ticagrelor, initiated on guideline-directed medical therapy for heart failure and referred to cardiopulmonary rehabilitation with aggressive lifestyle modifications.

At outpatient follow-up, patient was doing well without cardiac symptoms. Prior to the myocardial infarction, the original plan from oncologic was to initiate letrozole, an AI, for adjuvant therapy. Alternative treatment with tamoxifen was considered, however felt to be suboptimal secondary to thrombotic risk and inferiority to letrozole for recurrence of breast cancer. After discussion with the patient's primary oncologist, the decision was made to defer initiation of letrozole for 12 months, while the risk of recurrent cardiovascular events was highest. Additionally, the decision was made to continue DAPT for an additional year following the initiation of letrozole. Atorvastatin was initiated, but hepatic enzymes became abnormal and thus the therapy was discontinued. This posed a significant challenge as it is well known

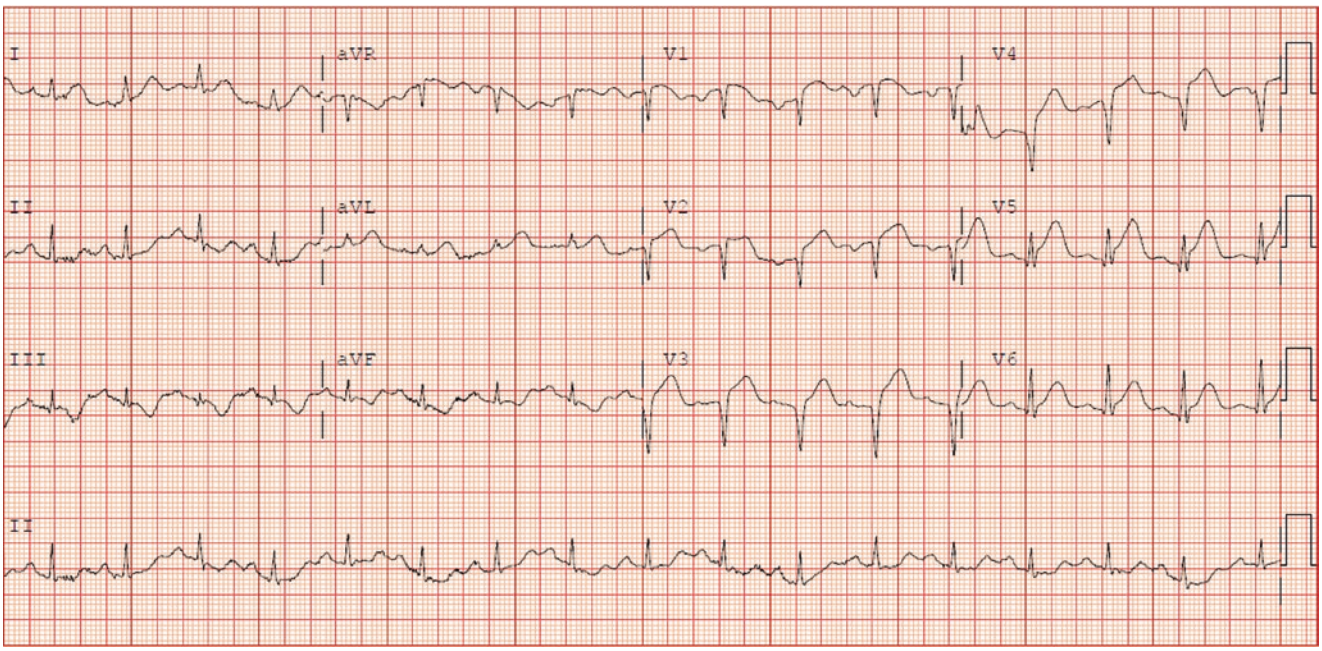

Fig. 21.2 12-lead ECG on presentation revealing anterior ST elevations

that letrozole (as well as other AIs) impacts lipid profiles. Alternative therapies such as evolocumab are being considered.

Case Discussion

We describe the case of a postmenopausal woman with recent diagnosis of ER+ HER2- breast cancer presenting with anterior STEMI and underwent PCI with drug-eluting stent placement. This is a patient with known nonobstructive coronary disease by CTA within a year prior to her MI event. Whether pre-existing atherosclerotic coronary disease contributed to this patient's presentation in the setting of heightened inflammation secondary to cancer is unclear. However, it is known that patients with cancer are at elevated risk of arterial thromboembolic (ATE) events manifesting as ischemic heart disease and stroke within the first several months after cancer diagnosis.

Following the management of her acute coronary syndrome, her treatment teams then needed to address long-term management of cancer and cardiovascular disease. Unfortunately, there are no current guidelines that address the vast majority of management decisions for a cancer patient experiencing an ATE event. There are infinite variables requiring risk and benefit analysis. For example, a large meta-analysis suggested the lack of survival benefit for AI over tamoxifen in breast cancer, even with longer cancer-free periods, may be secondary to the increased risk of cardiovascular events with AI. This elevated risk was amplified in women with pre-existing cardiovascular disease [3]. *Furthermore, several studies have found an association of unfavorable changes in lipid profile for patients on letrozole* vs *tamoxifen* [4, 5]. *This data would suggest consideration of switching letrozole to tamoxifen for patients with elevated cardiovascular risk. However, others would argue that the overall risk of cardiovascular events in both letrozole and tamoxifen is consistently low in both trial arms, and this must be weighed against the elevated risk of venous thrombosis with tamoxifen as well as the established superiority of AI in decreasing cancer recurrence* [3, 4, 6].

A common dilemma in the setting of myocardial infarction or thromboembolic stroke is selection of antiplatelet or anticoagulation regimen. The risk of thrombosis must be weighed against the propensity for bleeding in the setting of thrombocytopenia, platelet dysfunction, and anemia. The Society for Cardiovascular Angiography and Interventions published a consensus statement for cancer patients undergoing PCI, focusing mostly on thrombocytopenic patients with elevated bleeding risk. Recommendations included platelet cutoff values for each antiplatelet agent and dosing, as well as reduced duration for DAPT when platelet count <50,000 [7].

However, it is important to note that cancer patients have an increased risk of stent thrombosis, even on DAPT [8, 9]. *Furthermore, several chemotherapy agents can negatively affect stent endothelialization secondary to the cytostatic and cytotoxic properties* [10]. *Vascular endothelial growth factor (VEGF) is an important molecule in negating restenosis, and therefore VEGF inhibitor therapies have been hypothesized to also increase risk of stent restenosis, although adequate data is lacking* [10].

Ultimately, without large randomized controlled trials and data that can be easily extrapolated to a specific patient, management for acute ATE events in cancer patients will continue to require an individualized approach. For our patient, interdisciplinary discussion between cardiology, oncologic, and the patient was critical in complex decision-making. In this patient, given her low risk of cancer recurrence and low bleeding risk, a cautious approach of delaying AI for 12 months post-MI and extending DAPT for an additional 12 months was pursued.

Arterial Thrombosis

As described in the case, patients with underlying malignancies are at increased risk for arterial thrombosis. This risk is related to the frequent presence of a prothrombotic milieu in patients with cancer and/or to the direct adverse vascular and thrombogenic effects of various cancer treatments. Several mechanisms have been postulated to account for the occurrence of arterial thrombotic events, but the pathophysiology remains incompletely understood. However, it is appropriate to conceptually frame the discussion by separating the causes of arterial thrombosis secondary to the cancer itself from those associated with cancer treatment.

Secondary to Cancer

While the association between cancer and venous thromboembolism has been recognized for over a century, the increased risk of arterial thrombosis has been more recently appreciated. In particular, recent data from the Surveillance, Epidemiology, and End Results-Medicare database indicate a significant increase in arterial thromboembolism, including myocardial infarction [11]. These authors compared 279,719 patients with the most common types of malignancies in the United States (breast, lung, prostate, bladder, pancreatic, gastric, and colorectal cancer and non-Hodgkin lymphoma) with age- and sex-matched controls. At 6-month follow-up, patients with cancer had a substantially increased risk of arterial thromboembolism (composite of myocardial infarction and stroke) compared to controls: 4.7% (95% confidence interval [CI], 4.6% to 4.8%) versus 2.2% (95% CI, 2.1–2.2%) (hazard ratio, 2.2; 95% CI, 2.1–2.3), respectively. The risk was greatest in patients with lung cancer compared to other types of cancer and in patients with more advanced stages of cancer [12]. The hypercoagulable state observed in patients with cancer is likely mediated by a diverse array of mechanisms rather than a single common pathway. Cancer-related factors include elevated neutrophil and platelet count, enhanced tissue factor expression, release of microparticles, and increased inflammatory mediators. Neutrophils can contribute to thrombus formation by extruding neutrophil extracellular traps (NETs), which consist of strands of nuclear chromatin, granular proteins, and proteases. NETs have been shown to directly activate the contact pathway, inhibit thrombomodulin, and promote red blood cell and platelet adhesion. In addition to high neutrophil count, patients with cancer frequently present with elevated platelet count, a known risk factor for VTE. Circulating microparticles are small spherical cellular fragments released from the plasma membrane of various cells. They may trigger thrombosis secondary to their high levels of tissue factor and by providing negatively charged phospholipids [13, 14].

Secondary to Cancer Therapy

Various cancer treatments are associated with an increased risk of venous and arterial thrombosis [14]. The mechanisms underlying this risk are complex and involve effects on the vascular endothelium, on the coagulation pathways, and on metabolic risk factors. Direct endothelial cell injury, such as from platinum-based agents, antimetabolites (5-FU), antimicrotubule agents (paclitaxel and vinblastine), and antitumor antibiotics (bleomycin), is likely the main mechanism whereby these agents increase thrombotic risk. In addition, VEGF inhibitors such as bevacizumab and VEGF-signaling pathway inhibitors such as sorafenib and sunitinib have also been associated with arterial thrombosis, probably related to their effects on endothelial function [15].

Premature Coronary Artery Disease

Secondary to Pharmacologic Therapy

While there is scant evidence that cancer therapy is directly a cause of atherosclerosis, several treatments have long-lasting endothelial and metabolic effects that may predispose to the development of premature atherothrombosis. For example, patients who previously received cisplatin-based chemotherapy for testicular cancer had increased risk of developing lipid disorders, obesity, and hypertension [16].

As mentioned previously, AI therapy has been associated with adverse cardiovascular events, likely secondary to the impact on serum cholesterol. It is proposed that the decreased levels of estrogen during adjuvant hormonal therapy have downstream effects on HDL and LDL levels. Not all AI agents have the same effect, which may be explained by varying modes of action. Anastrozole and letrozole are non-steroidal reversibly binding AIs. Letrozole has been associated with adverse effects on lipids, including increased LDL and total cholesterol. Anastrozole has little to no effect on lipids. By contrast, exemestane, a steroidal irreversibly binding AI, demonstrated a slight positive impact on lipids in clinical trials [17]. Of note, tamoxifen has estrogenic agonist effects on lipid profiles, with several studies showing a decrease in total and LDL cholesterol and mild increase in HDL [17, 18]. A recent large cohort-based retrospective

analysis found an association of increased risk of myocardial infarction (HR = 2.08; 95% CI, 1.02, 4.27) but not cardiovascular mortality (HR = 0.87; 95% CI, 0.49, 1.54) when comparing patients switching from tamoxifen to AI vs continuing tamoxifen therapy [19]. Although there are no specific guidelines for management of hypercholesterolemia in this context, close lipid monitoring and identification of high-risk patients are crucial. Adherence to ACC/AHA guidelines is advisable for patients undergoing hormonal therapy to optimize cardiovascular risk management [20]. In special cases consideration of alternative hormonal therapy is reasonable.

Secondary to Radiation Therapy

Radiation therapy is an integral part of treatment in over 50% of patients with cancer and should be readily queried in the history obtained in the ED. Unfortunately, the effects of radiation are nonselective, and vessels within the field of radiation are vulnerable to acute injury, leading to endothelial dysfunction, inflammation, and thrombosis, as well as to long-term damage, with premature atherosclerosis and extensive calcification [21]. The clinical manifestations of radiation-induced vascular damage depend on the area of exposure. Radiation to the chest, such as for Hodgkin's lymphoma and breast cancer, has been associated with increased risk of premature CAD, whereas head and neck radiation confers a higher risk of carotid disease, transient ischemic attack, and ischemic stroke [22–26]. In support of this evidence, in 5-year survivors of childhood cancer, an average radiation dose exceeding 5 Gy is associated with a significant increase of risk of dying from cardiac disease [27]. Furthermore, patients who received mediastinal irradiation for Hodgkin's lymphoma had a 3.2-fold increased risk of requiring surgical coronary revascularization, a 1.6-fold risk of needing endovascular coronary procedure, and a 9.2-fold risk of requiring valve surgery [28]. Most modern radiotherapy programs have been able to deliberately exclude cardiac substructures from direct beam paths as part of the computer-based and image-guided treatment planning process.

Coronary Artery Vasospasm

The fluoropyrimidines antimetabolite 5-fluorouracil (5-FU) and its oral prodrug capecitabine are first-line agents for the treatment of head and neck, breast, and gastrointestinal cancers. One of the most concerning toxicities of 5-FU and capecitabine is the occurrence of coronary vasospasm, leading to ischemia, angina, myocardial infarction, arrhythmias, or sudden death. Postulated mechanisms of fluoropyrimidine-mediated vasospasm include endothelial dysfunction, with increased bioactivity of the potent vasoconstrictor endothelin-1, cytolysis with denudation of the intima, and enhanced smooth muscle cell contractility [14]. Coronary vasospasm is a medical emergency and requires prompt medical attention and treatment. Given the primary role of fluoropyrimidines in the treatment of various malignancies, in patients who develop vasospasm, rechallenge may be considered with the use of cardioprotective pretreatment [29].

Vasculitis

The introduction of immunotherapies, which harness the body's own defense system to attack malignant cells, has represented an unprecedented leap forward in the treatment of a growing number of cancers. In particular, immune checkpoint inhibitors (ICIs) have shown high rates of sustained response in various malignancies and are now considered also as first-line therapy. However, the enhancement of immune responses has been associated with the occurrence of a wide range of autoimmune phenomena, with reported involvement of most organs. While less common than other manifestations, the involvement of the cardiovascular system has been of significant concern, as mortality in patients with ICI-mediated myocarditis is as high as 50%. In addition to myocarditis and pericarditis, vasculitides have also been reported in association with ICI. Any vascular bed can potentially be affected, but large vessel vasculitis of the aorta and temporal arteries are most commonly reported. As such, the ED practitioner should consider this as a possible etiology when evaluating known cancer patients for an acute presentation consistent with systemic vascular inflammation. Importantly, patients with temporal arteritis are at risk of permanent visual loss and require prompt treatment with high-dose steroids [30].

Peripheral Artery Disease

Secondary to Pharmacologic Therapy

Tyrosine kinase and VEGF-signaling pathway inhibitors represent important therapeutic classes and have revolutionized management of several cancers. However, their use has been associated with unpredictable and at times severe vascular toxicity including hypertension, stroke, arterial thrombosis, and aortic dissection [14, 31]. Dasatinib has been linked to the development of pulmonary arterial hypertension, whereas nilotinib and ponatinib have been associated with an increased risk of myocardial ischemia, cerebrovascular accidents, and peripheral artery disease, in some cases requiring revascularization or leading to amputation. Of note, while the vascular toxicity of nilotinib may be related, at least in part, to its adverse effects on body weight and on glucose and lipid metabolism, the vascular toxicity of ponatinib appears to be a new form of microvascular angiopathy [32].

Table 21.1 Chemotherapeutic agents associated with HTN and VTE and the incidence of each

Drug class	Chemotherapeutic agent	Clinical use	Hypertension incidence (%)	VTE incidence (%)
Alkylating agents	Cisplatin	Bladder, breast, head and neck, lung, ovarian, testicular	14–53	8.5–12.9 (74% cases within first 2 cycles)
Histone deacetylase inhibitors	Vorinostat	Cutaneous T-cell lymphoma	–	4.7–8
Immunomodulators	Thalidomide	Multiple myeloma	–	<5–58
	Lenalidomide		–	3–75
VEGF-signaling pathway inhibitors	Bevacizumab	Colon, ovarian, cervical, lung, renal cell, hepatocellular, thyroid, sarcoma	26–55	8–14
	Axitinib		40	3
	Cabozantinib		22–37	4–6
	Lenvatinib		41–68	–
	Pazopanib		35–57	2–5
	Sorafenib		17–48	5.5
	Sunitinib		16–47	0.5–3
Tyrosine kinase inhibitors Bcr-Abl	Bosutinib	Chronic myeloid leukemia, sarcoma	7.8	–
	Dasatinib		<10	–
	Imatinib		4	–
	Ponatinib		67	5–27
	Nilotinib		8–10	–
EGFR	Erlotinib	Lung	–	1.2–11

Secondary to Radiation Therapy

As introduced above, radiation therapy induces extensive vascular wall injury. The biological consequences of this damage extend beyond the acute phase and lead to progressive abnormal remodeling, increased susceptibility to atherosclerosis (also in the absence of traditional risk atherosclerotic risk factors), and extensive calcific degeneration. The clinical manifestations usually reflect the occurrence of hemodynamically significant stenoses in various arteries (e.g., brachiocephalic, subclavian, renal, iliac) and the presence of severe calcifications (e.g., porcelain aorta with inability to perform coronary bypass surgery). Of note, the risk of radiation-induced vascular injury increases with young age at time of exposure, higher total cumulative dose, higher dose of radiation fractions, concomitant cancer treatment, and superficial location of the vessels [23–25].

Non-ischemic Vascular Conditions

Of the non-ischemic vascular disorders, hypertension and venous thromboembolism (VTE) are especially important, because (i) many antiangiogenic drugs, especially vascular endothelial growth factor inhibitors (VEGFIs), induce development of hypertension; (ii) some anticancer treatments promote thrombogenesis and coagulation; and (iii) the underlying cancer itself is a prothrombotic condition. VEGFI-induced hypertension develops rapidly, is often severe, and may be associated with posterior reversible leukoencephalopathy, a medical emergency [33]. Cancer-associated VTE is especially prevalent in metastatic disease and is often associated with comorbidities such as atrial fibrillation. An overview of classes of chemotherapy agents most commonly associated with the non-ischemic cardiovascular toxicity emergencies – hypertension and VTE – will be highlighted, including alkylating agents (e.g., cisplatin), histone deacetylase inhibitors (e.g., vorinostat), immunomodulators (e.g., thalidomide), and tyrosine kinase inhibitors (TKIs), which include inhibitors of Bcr-Abl, endothelial growth factor receptor (EGFR), and VEGF (Table 21.1). We will also address strategies in the prevention, diagnosis, and management of these conditions in the emergency setting.

Hypertension

Hypertension (HTN) is a common comorbidity in cancer patients (37%) [34]. Newer more-targeted cancer therapies such as VEGFI have been associated with an increased risk of HTN. Almost every clinical trial of VEGFI reports a treatment-associated rise in blood pressure. Furthermore, up to 80% of patients develop HTN, either de novo or worsening of previously controlled disease [35].

The clinical consequences of VEGFI-associated HTN can be severe. The rapid onset of HTN in patients not previously "conditioned" to high blood pressure can lead to end-organ complications, such as stroke, myocardial ischemia, heart failure, and acute kidney injury, and proteinuria. Furthermore, VEGFIs have been associated with the development of posterior reversible encephalopathy syndrome (PRES), charac-

terized by headaches, confusion, visual impairment, and seizures [33]. These manifestations, however, may be reversible with prompt recognition and treatment of the severe hypertension.

Mechanisms underlying VEGFI-induced HTN are incompletely understood. However, VEGF inhibition leads to a reduction of vasodilator, nitric oxide (NO), and is associated with increased production of the vasoconstrictor, endothelin-1 [36, 37]. Other hypotheses include oxidative stress, capillary rarefaction, and activation of the renin-angiotensin-aldosterone system (RAAS) [38]. Oxidative stress and excessive reactive oxygen species (ROS) production can lead to a reduction in NO bioavailability. Rarefaction is a reduction in density of arterioles and capillaries, and marked reductions in capillary density have been demonstrated with VEGF inhibition, although it is uncertain if this is a cause or effect of VEGFI-associated HTN. The role of RAAS activation is unclear as VEGFIs have been associated with a decrease in renin levels and angiotensin-converting enzyme (ACE) inhibition has a limited impact on VEGFI-associated HTN.

Diagnosis

The Cardiovascular Toxicities Panel of the National Cancer Institute recommends frequent monitoring of blood pressure, particularly during the first cycle of treatment. Home blood pressure monitoring and 24-hour ambulatory blood pressure monitoring should be pursued, where feasible, to diagnose and monitor HTN, with blood pressure ≥140/90 mmHg defined as HTN [34].

Treatment

Prior to commencing cancer treatment, adequate blood pressure control (<140/90 mmHg) should be achieved in patients with pre-existing HTN. Patients with blood pressure ≥140/90 mmHg should be treated with antihypertensive therapy. VEGFI-induced HTN can be difficult to treat and may require multiple agents to achieve blood pressure control. The choice of antihypertensive agents generally follows national guidelines for first-line treatment of HTN, and there is no evidence of superiority of one agent over another. However, non-dihydropyridine calcium channel antagonists such as verapamil and diltiazem inhibit cytochrome P450 3A4 and should be avoided secondary to the potential for consequent VEGFI toxicity. ACE inhibitors or angiotensin receptor blockers (ARBs) may be of benefit in patients with left ventricular dysfunction or proteinuria. Other agents such as dihydropyridine calcium channel antagonists, beta-blockers, and diuretics can also be used. There is some evidence that phosphodiesterase inhibitors, NO donors, and endothelin-1 receptor antagonists may be effective; however, these have not been studied extensively in clinical trials. End-organ complications of VEGFI-induced HTN should be managed as per existing guidelines. PRES is diagnosed with magnetic resonance imaging of the brain revealing characteristic posterior fossa changes on T2-weighted imaging reflecting edema. Treatment is largely supportive, with blood pressure control and withdrawal of VEGFI therapy and antiepileptic therapy to treat seizures.

Venous Thromboembolism

Cancer is a prothrombotic condition, and VTE risk appears to be greatest in those with distant metastases and established VTE risk factors. Independent risk factors include central venous catheters, immobility, heart failure, and chemotherapy [39].

The pathophysiological processes associated with VTE in cancer include secretion of inflammatory cytokines and interaction with endothelial cells and platelets with activation of clotting cascade, particularly via increased TF expression. Additionally, there is inhibition of anticoagulant factors such as activated protein C and thrombomodulin, as well as reduced fibrinolysis [40].

Cancer therapies can further contribute to the prothrombotic state from direct damage to the endothelium and cancer cells, inducing apoptosis and releasing inflammatory cytokines. Additionally, they increase the activity of procoagulants such as TF and reduce the production of anticoagulants such as protein C and antithrombin from direct hepatotoxicity [39]. Cisplatin-associated VTE may be induced by direct endothelial injury, vascular inflammation, hypomagnesemia-induced vasospasm, increased procoagulant activity, and reduced anticoagulation formation [41]. Thalidomide and its analogues increase levels of von Willebrand factor and, when used in combination with anthracyclines, have been shown to induce endothelial dysfunction and increase levels of TF [42]. TKIs have also been shown to increase levels of von Willebrand factor and TF reflecting activation of endothelial cells [43].

Diagnosis

DVT is diagnosed by compression Doppler ultrasonography which can readily be acquired in the ED, while the gold standard for PE diagnosis is spiral CTA of pulmonary vessels. Nuclear medicine techniques such as ventilation/perfusion scans and magnetic resonance imaging angiography are alternative options for those with contraindications to computed tomography (CT).

Prevention

Generally, thromboprophylaxis should not be offered to ambulant patients with cancer. However, it may be consid-

ered in high-risk patients and those with other risk factors for VTE such as obesity, previous VTE, central venous catheters, and immobility. The Khorana risk score is used to stratify the risk of VTE in cancer patients. This takes into consideration the type of cancer, platelet count, hemoglobin, and body mass index (BMI), with a score ≥3 classified as high risk [44]. Thromboprophylaxis with low molecular weight heparin (LMWH) or direct oral anticoagulants (DOACs) should be offered, taking bleeding risk and drug interactions into consideration. DOAC therapy has been associated with increased risk of bleeding with gastrointestinal and genitourinary malignancies. Patients treated with thalidomide and dexamethasone or anthracycline chemotherapy should also be considered for prophylaxis with aspirin (75–150 mg), low molecular weight heparin (LMWH), or direct oral anticoagulants (DOACs) [45].

Treatment

The American Society of Clinical Oncologic guidelines recommend treatment of cancer-associated VTE with LMWH or DOAC therapy. These are preferred over vitamin K antagonists secondary to improved efficacy. The American College of Emergency Physicians recommends treatment of VTE with vitamin K antagonists or LMWH, and the use of DOAC therapy as an alternative. However, no recommendations have been made specifically for cancer patients [46]. Anticoagulation treatment should continue for at least 6 months, with duration of treatment beyond this dependent on risks and benefits for individual patients.

Pericardial Diseases

Malignant involvement of the pericardium is detected in 1–20% of autopsy studies of cancer patients, and the spectrum of the acute clinical presentation can include acute pericarditis, pericardial effusion with or without cardiac tamponade, or effects of local cancer invasion (primary or secondary). Additionally, pericardial disease in cancer patients can be as a result of their cancer treatment, such as cytotoxic chemotherapy and/or radiotherapy. Determining the etiology and providing effective treatment can often be challenging. The natural history of pericardial diseases in the oncologic setting can be complicated with pericardial emergencies requiring prompt diagnosis, procedural intervention, intensive care with hemodynamic monitoring, and early aggressive management.

Pericarditis

Pericarditis is the commonest form of pericardial disease and is responsible for around 5% of presentations to emergency departments with non-ischemic cardiac pain [47, 48]. Mortality rates can reach 1% [49].

Acute Pericarditis

Acute pericarditis can present a medical emergency manifesting with symptoms such as intense sharp chest pain, alongside other diagnostic signs such as pericardial friction rub, and widespread saddle-shaped or concave ST segment elevation on the electrocardiogram (ECG), with or without a pericardial effusion. At least two of the four aforementioned features should be present to make the diagnosis [50]. In an unselected cohort of pericarditis patients, approximately 5% of cases were attributable to underlying cancer [48]. This may develop via direct infiltration of malignant cancer cells via adjacent structures, pericardial hemorrhage, or hematogenous dissemination of cancer cells [51]. In addition, pericarditis may occur as part of the paraneoplastic syndrome. In some instances, it can be caused as an acute side effect of radiation therapy. This acute phase is mediated, in part, by tumor necrosis factor (TNF) and interleukins (IL) IL-1, IL-6, and IL-8, further leading to neutrophil infiltration [24].

Alongside markers of inflammation such as C-reactive protein and erythrocyte sedimentation rate (ESR), diagnosis of cancer as the cause of pericarditis requires imaging (e.g., CT scan or cardiac magnetic resonance (CMR) imaging), cytology of pericardial fluid, and, ultimately, biopsies confirming malignant infiltration within the pericardial tissue.

The treatment of acute pericarditis is usually as per recommended guidelines in the general population. However, it is to be recognized that many cancer patients may have a predisposition to bleeding due to abnormal blood counts or coagulation abnormalities secondary to their disease or treatment. It can thus be challenging to introduce routine therapy such as nonsteroidal anti-inflammatory agents in this context. As a result, there is often a greater and earlier use of other agents, e.g., colchicine and steroids, although this may not alter outcomes [49]. In the case of radiotherapy-induced acute pericarditis, treatment of primary malignancy should not be withheld because of this.

Immunotherapy-Induced Pericarditis

Adverse effects of ICIs are distinct from conventional cytotoxic chemotherapy and can be life-threatening if left unrecognized. Pericarditis is an infrequent cardiac toxicity of ICIs and can occur with coexisting myocarditis. A total of seven cases of ICI-associated pericardial disease have been described, two involved ipilimumab and five involved nivolumab [52]. The exact mechanisms underlying ICI-mediated pericardial disease remain unknown; however, they might include pericardial inflammation by ICI-stimulated cytotoxic T-cells.

The treatment regimens for ICI-associated pericarditis vary depending on the case; however, the principal strategy

concentrates on targeting the hyperactive T-cell response with steroids often used as first-line agents.

Pericardial Effusion

Cardiac tamponade is the ultimate emergent complication of pericardial effusion, and is an absolute indication for urgent drainage, either by pericardiocentesis, a surgical pleuropericardial window, or by surgical pericardiotomy. Tamponade develops when the pericardial fluid pressure is greater than the intracardiac filling pressures, compromising the cardiac filling and leading to reduced cardiac output and cardiogenic shock. Patients may present acutely unwell with presyncopal symptoms, dyspnea, orthopnea, chest pain, and/or arrhythmias. Clinical findings include sinus tachycardia, jugular venous distention, pulsus paradoxus (>10 mmHg drop in systolic blood pressure during inspiration), lower extremity edema, hypotension, and, eventually, circulatory collapse. ECG findings include low-voltage QRS complexes, electrical alternans (alternating amplitude or axis of the QRS complexes between each cardiac cycle), PR segment depression, and sinus tachycardia. Echocardiography is the diagnostic test of choice since it can help with establishing the diagnosis and also guide management.

Although malignant pericardial effusion can occur as an early manifestation, they are usually a late finding in patients with metastases. This condition usually occurs because of obstruction of lymphatic drainage or an excess of fluid secretion from tumor nodules on the pericardial surface. The majority of patients are asymptomatic, and the effusion is discovered incidentally on echocardiography ordered for other reasons during their treatment. The mainstay of treatment is to allow sufficient drainage of the pericardial fluid to relieve the symptoms and prevent recurrence. Pericardiocentesis is an easier and less invasive procedure than pericardial window surgery, allowing prompt treatment at the time of diagnosis. However, pericardiocentesis leads to a recurrence rate of up to 20% at 30 days, which is higher than recurrence after surgical drainage (1–10% of recurrence) [53]. Rarely, malignant pericardial effusions are managed with intrapericardial injection of chemotherapeutic agents.

Cytotoxic chemotherapy agents themselves are also associated with pericardial diseases. Traditional chemotherapy agents such as fludarabine, cytarabine, doxorubicin, docetaxel, and cyclophosphamide have been associated with acute pericarditis and pericardial effusion [54, 55]. Dasatinib, a TKI targeting BCR-ABL, has also been linked to an increased incidence of pericardial effusions.

In rarer cases, primary neoplasms of the pericardium such as malignant mesotheliomas and angiosarcomas can cause primary pericardial effusions via direct invasion and are associated with a poor prognosis. Specific to angiosarcomas, patients often present with pericardial effusions and/or in cardiac tamponade in about 56% of cases. Angiosarcomas are mostly resistant to chemotherapy and radiotherapy and necessitate surgical therapy.

Cardiomyopathies

Systolic Cardiomyopathy

Systolic cardiomyopathy (CM) has long been associated with traditional cytotoxic chemotherapeutic agent toxicity. In addition, thoracic radiation therapy (XRT), newer molecular-targeted agents, and immune checkpoint inhibitors (ICI) have been shown to produce left ventricular (LV) systolic CM (traditionally defined as reduction in LV ejection fraction [LVEF] by at least 10%, even if LVEF is >50%) in recent years. Systolic CM is divided into four stages: stage A is defined as exposure to a known cardiotoxin, stage B is asymptomatic LV dysfunction, and stages C and D are defined as symptomatic heart failure (HF) to end-stage HF [56]. The main agents causing systolic CM are summarized in Table 21.2 [25, 58–64]. Risk factors common to all classes include age (>65 or < 10 years old), uncontrolled hypertension, smoking exposure, pre-existing diabetes, and baseline systolic LV dysfunction (LVEF <50%) [56].

Stress Cardiomyopathy

Of the agents in Table 21.2, some have been shown to cause acute stress CM related to initial dose [58, 60]. This has especially been studied in anthracyclines. The incidence of stress CM in all cancer patients is up to 10%, which may be related to chemotherapy and XRT use [61]. Cyclophosphamide >140 mg/kg or >1.55 g/m^2/day is known to cause acute systolic CM by mechanism of acute myopericarditis, which can be hemorrhagic. Rituximab has been shown to cause acute infusion-related cardiogenic shock [61]. Sunitinib and sorafenib can cause stress CM with stress-induced angiogenesis [64]. Antimetabolites such as 5-fluorouracil; clofarabine and capecitabine; lomustine + bevacizumab + cyclophosphamide + etoposide; rapamycin; interferon alpha; and trastuzumab have demonstrated an ability to cause cardiogenic shock secondary to stress CM, requiring ionotropic agents in up to 20% of patients [61].

Immune Checkpoint Inhibitor-Induced Cardiomyopathy

Adverse cardiac events associated with ICI therapy are rare (less than 1% of patients) but can be potentially life-threatening. The most common and well characterized is

Table 21.2 Systolic cardiomyopathies

Class	Agents and incidence [58, 61]	Mechanism [58–61, 63]	Class-specific risk factors[a] [25, 57, 60, 62, 64]
Anthracyclines and analogues	Doxorubicin Epirubicin Idarubicin Mitoxantrone Class Inc: 3–48%	Multiple-stress theory: ROS via iron chelation Nucleus topoisomerase IIB activation Iron overload Inhibition of DNA repair	Cumulative dose: Doxorubicin >360 mg/m^2 Daunorubicin >800 mg/m^2 Epirubicin >720 mg/m^2 Idarubicin >150 mg/m^2 Mitoxantrone >160 mg/m^2 Concomitant XRT Renal dysfunction, female sex
Monoclonal antibodies	Trastuzumab (HER2 target): 1–20%	Interruption of ErbB signaling, upregulated by ROS	Concomitant or prior anthracycline use
Alkylating agents	Cisplatin Cyclophosphamide Ifosfamide Class Inc: 7–38%	Direct endothelial and DNA injury Lipid peroxidation ROS Hemorrhagic myopericarditis	Usually during initial dose Dose-related (>140 mg/kg), irreversible in up to 25% at dose >1.55 g/m^2/day
Antimetabolites	5-Fluorouracil: 1–68% Capecitabine: 5.5%	Apoptosis of myocardial and endocardial cells Myocarditis Angiogenesis inhibitors Coronary vasospasm Cardiac arrhythmias	Usually during drug infusion Concomitant cisplatin use
Antimicrotubules	Paclitaxel Docetaxel Class Inc: 2–13%	NCS-1 activation → calcium overload	Concomitant anthracycline use
Proteasome inhibitors	Bortezomib: 25–% Carfilzomib: 42–8%	NF-κβ suppression	Baseline subclinical heart disease, measured by GLS
Protein kinase inhibitors, with tyrosine kinase inhibitors	Dasatinib: 3–29% Lapatinib, imatinib mesylate, cobimetinib, vemurafenib, trametinib, ibrutinib Inc: <1%	Mitochondrial damage Intrinsic apoptotic pathway	a
Vascular endothelial growth factor receptor inhibitors (VEGFR TKIs)	Sorafenib Sunitinib Lenvatinib Pazopanib Regorafenib Class Inc: 1.5–14%	Inhibits platelet-derived growth factor Inhibits nitric oxide generation → myocardial stress	Direct myocardial toxicity amplified by hypertension
Monoclonal antibody VEGFR	Bevacizumab Class Inc: 2–4%	Activated tissue factor release Prevention of endothelial regeneration	History of arterial thrombotic events
Immune checkpoint inhibitors	Nivolumab Pembrolizumab Ipilimumab Atezolizumab Durvalumab Class Inc of myocarditis 0.27%–1.14%	Out of those who develop myocarditis, ~50% present with systolic cardiomyopathy	Combination of ICIs[b]
Radiation therapy	N/A	Endothelial damage Acceleration of CAD ROS Fibrosis Sustained inflammation via NF-κβ	Age at XRT (>50 y); anterior or left chest XRT; concomitant chemotherapy with anthracyclines; high cumulative dose of XRT fractions (>2 Gy/day) or total dose >30 Gy; pre-existing CAD

CAD coronary artery disease, *ErbB/HER2* human epidermal growth factor receptor 2, *GLS* global longitudinal strain, *Gy* Gray, *ICIs* immune checkpoint inhibitors, *Inc* incidence, *NCS-1* neuronal calcium sensor 1, *NF-κβ* nuclear factor j-light-chain-enhancer of activated B-cells, *ROS* reactive oxygen species, *TKIs* tyrosine kinase inhibitors, *VEGFR* vascular endothelial growth factor receptor, *XRT* radiation therapy

[a]Risk factors common to all classes include age (>65 or <10-year-old), uncontrolled hypertension, smoking exposure, pre-existing diabetes, and baseline systolic LV dysfunction (LVEF <50%) [56]

[b]Note early versus late ICI toxicity described in text

ICI-induced acute fulminant myocarditis which typically occurs within 90 days of initiation of therapy, and is often associated with acute hemodynamic failure and death in up to 50% of patients [63]. The most commonly used and studied are nivolumab, pembrolizumab, and ipilimumab. Animal models suggest cardiac dysfunction may occur secondary to autoimmune response to cardiac troponin-I in PD-1-deficient mice via stimulation of calcium ion influx [65]. Fulminant myocarditis is more common in those receiving combination therapy ICI compared to monotherapy and is also associated with higher mortality rates [63].

Late ICI cardiac adverse effects have just begun to be examined. In a recent retrospective cohort study, late ICI cases (defined as >90 days after therapy initiation) revealed significantly more LV systolic dysfunction in 73.7% of cases (described as LVEF drop of >10% or LVEF <50%, with or without HF symptoms) than early ICI cases, and significantly higher rates of symptomatic HF (47% versus 21%, respectively; p = 0.01) [66]. Though overall mortality rates were not different between the two groups, it is important to be aware of the two clinically separate entities of ICI-induced cardiotoxicity.

Diastolic and Restrictive Cardiomyopathy

Radiation Therapy

XRT may cause systolic or diastolic dysfunction, with diastolic dysfunction being more common [25]. One single-institution study found that of 294 asymptomatic patients with Hodgkin's lymphoma treated with mediastinal XRT, 14% developed some form of diastolic dysfunction during the mean follow-up period of 3.4 years [67]. Factors that increase the risk of XRT-induced injury are shown in Table 21.2.

Acutely, XRT-induced inflammation results in mild myocardial dysfunction. Between 5 and 30 years post XRT, myocardial edema and inflammation directly lead to non-ischemic myocardial fibrosis [26]. The rate of ischemic heart disease, including myocardial infarction, is known to increase after mediastinal XRT [59, 68]. Myocardial ischemia can compound concurrent myocardial dysfunction secondary to XRT-induced myocardial fibrosis, potentiating the risk for flash pulmonary edema and acute progression to advanced HF [67]. XRT may lead to restrictive CM several years to decades after exposure [61].

In the Framingham study, systolic and diastolic dysfunctions after XRT were found in 13%, 18%, and 29% of patients with latency periods of 2–10, 11–20, and >20 years, respectively, compared to age-matched controls without XRT [60]. Authors did not assess for prior anthracycline use [21].

Anthracyclines and Monoclonal Antibodies

The effects of chemotherapy on diastolic dysfunction remain incompletely defined. In a recent longitudinal cohort study of 364 breast cancer patients, doxorubicin or doxorubicin followed by trastuzumab therapy was shown to produce diastolic dysfunction at 60% in 1 year, 70% by 2 years, and 80% by 3 years, with diastolic dysfunction shown to correlate with reduction in LVEF (2.1%; $p < 0.001$), and global longitudinal strain (GLS) (0.6%; p 0.013) [69]. Trastuzumab alone was not associated with diastolic dysfunction. Further studies are needed to determine long-term risk of HF in this population [69].

Cardiomyopathy Diagnosis

Cardiac dysfunction in oncologic patients and survivors is diagnosed by careful monitoring of the LV. Baseline LVEF and quantitative evaluation of diastolic dysfunction should be measured before treatment [56]. GLS should be measured in those with baseline GLS monitoring [56, 62]. Though routine use of cardiac biomarkers to detect CM is not well-established, some biomarkers such as troponin levels have been shown to predict CM in high-risk patients, such as those with pre-existing cardiovascular disease and those receiving high-dose anthracyclines [56]. In the most recent largest prospective study of patients treated with anthracyclines and/or trastuzumab, high sensitivity cardiac troponin T >14 ng/L at completion was associated with a twofold risk of CM, N-terminal pro-B-type natriuretic peptide (NT-proBNP) was shown to predict CM in sequential anthracycline-trastuzumab therapy, and myeloperoxidase was shown to be a promising new biomarker for anthracycline-induced CM [70].

For CM associated with ICI, early recognition and diagnosis of ICI-related myocarditis are critical secondary to its life-threatening potential. Shortness of breath is the most common presenting symptom [63]. Cardiac troponin appears to be a valid marker with a sensitivity of 94–100% [71]. Elevated NT-proBNP, peripheral edema, angina, and electrocardiogram abnormalities are common findings [63]. Severe conduction diseases including ventricular tachycardia and complete heart block are frequently seen.

Early detection in cardiogenic shock can be difficult as most patients have preserved LVEF, which can make diagnosis challenging. Whereas reduced LVEF may be a late finding, abnormal GLS may detect early evidence of cardiotoxicity not readily diagnosed by 2D echocardiography and can be a useful screening tool [62].

Cardiomyopathy Treatment

Patients who develop systolic LV dysfunction (LVEF <50%) or in stage B during anthracycline treatment should be treated with HF goal-directed medical therapy, including beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers [56, 57]. The most studied agents are carvedilol, metoprolol, and bisoprolol, with notable recent trials showing significant reduction of mean change in LVEF using candesartan versus metoprolol and placebo. Statins, aspirin, enoxaparin, and rivaroxaban/apixaban have some clinical trial data to suggest cardioprotection as well [56]. Other cardioprotective strategies for anthracyclines include choosing liposomal formulations, using less cardiotoxic ones – epirubicin, idarubicin, and mitoxantrone – and continuous rather than bolus administration [56, 57]. Dexrazoxane, a cardioprotective agent via iron chelation and topoisomerase II inhibition, may be used if cumulative doxorubicin is >300 mg/m^2 and/or the disease is metastatic [72]. In stage C and D HF, critical decision on withholding further chemotherapy, implantable cardioverter-defibrillator placement, cardiac resynchronization therapy, and more advanced measures of inotropic support to transplant are considered [56, 60].

For ICI, by recent guidelines, it is recommended to discontinue ICI therapy with any sign of cardiotoxicity [56, 73]. In patients with severe disease with hemodynamic compromise, intravenous prednisone 1–2 mg/kg, or methylprednisolone 500–1000 mg/kg, is recommended as first-line therapy. Addition of mycophenolate or infliximab can be considered in patients with suboptimal response to corticosteroids [74]. In corticosteroid-refractory cases, the use of antithymocyte globulin (ATG) and the combination of alemtuzumab and abatacept have been found to be effective [75, 76].

In cases of cardiogenic shock, treatment overall does not differ from that of the general population [61]. Ensuring hemodynamic stability is the first priority, and advanced mechanical circulatory support with extracorporeal membrane oxygenation or ventricular assist devices can be considered for patients with refractory cardiogenic shock and good life expectancy [61]. Treatment options for cardiogenic shock in the setting of fulminant XRT-induced myocarditis include immunoglobulin, ATG, tacrolimus, mycophenolate, and infliximab [61].

Ultimately, prevention of cardiotoxicity at the non-pharmacologic level should start before cancer treatment begins (before stage A), and with the help of a multidisciplinary team involving oncologic, cardiology, and immunology.

Myocarditis

ICIs are antibodies that enhance antitumor immunity by increasing the activation of T-cells [63, 77, 78]. Since the US Food and Drug Administration (FDA) approved the first ICI in 2011, the application of this immunotherapy has increased from late-stage malignancy to adjuvant and even first-line settings in early malignancy [77, 78]. The number of ICI therapies continues to grow. Nivolumab, pembrolizumab, and cemiplimab target the programmed cell death receptor-1 (PD-1); ipilimumab and tremelimumab target the cytotoxic T-lymphocyte antigen-4 (CTLA-4); and atezolizumab, avelumab, and durvalumab target the programmed cell death ligand-1 (PDL-1) [77]. Consequences of increased immune system activity include disrupted immunological homeostasis and resultant inflammatory disease of nearly every organ system, e.g., the gastrointestinal tract, endocrine glands, skin, muscle, and liver, with complications termed immune-related adverse events (irAEs) [77]. The severity of irAEs varies, based on the organ system involved. The spectrum of cardiovascular toxicity can include myocarditis, pericarditis, and vasculitis, among other conditions. Myocarditis in particular is associated with an elevated case fatality rate of up to 30–50% [63, 79].

Presentation

Data on myocarditis following ICI therapy are limited by their retrospective nature, given the relatively low prevalence of this irAE at up to 1.14% [63, 80]. Awareness of myocarditis as an irAE has been rising, with an increase in reporting incidence over time [81]. The median time from ICI initiation to myocarditis admission is 51 days [82], with 4 out of 5 patients presenting within the first 3 months [63]. Symptoms include chest pain, shortness of breath, fatigue, orthopnea, and paroxysmal nocturnal dyspnea [63]. Myocarditis can often occur with concomitant myositis, hepatitis, and myasthenia gravis [81]. In our experience, electrocardiographic changes include PR interval prolongation, QRS interval prolongation in a right bundle branch pattern progressing to high-grade atrioventricular conduction block and ventricular tachycardia. Troponin has been elevated in nearly 90% of cases and fourth-generation troponin T assay ≥1.5 ng/mL is associated with a fourfold increase in major adverse cardiovascular events (MACE; defined as a composite of cardiovascular death, cardiogenic shock, cardiac arrest, and hemodynamically significant complete heart block) [63]. LVEF measured by transthoracic echocardiogram (TTE) or cardiac magnetic resonance (CMR) is preserved in over one half of cases at presentation [63, 78]. However, subclinical left ventricular dysfunction in myocarditis patients is evident in the form of reduced GLS on TTE, such that myocarditis patients have a median 14% GLS, compared to normal GLS among controls without myocarditis. Furthermore, each percentage decrease in GLS is associated with a 1.5-fold increase in MACE among patients with a reduced EF and a 4.4-fold increase in MACE among patients with normal LVEF; GLS ≤14% is associ-

ated with the highest major adverse cardiovascular event (MACE) rate. GLS has been predictive of a nearly twofold increase rate of MACE in a multivariable model adjusted for EF [82].

Diagnosis

Suspected myocarditis patients with rising troponin should undergo emergent left heart cardiac catheterization, with left ventriculogram if possible, to rule out acute coronary syndrome and stress cardiomyopathy. If cardiac catheterization demonstrates nonobstructive coronary artery disease, we favor right ventricular endomyocardial biopsy as the gold standard for diagnosis of myocarditis, as a diagnosis of ICI-associated myocarditis could preclude further possibly life-prolonging ICI cancer therapy. Endomyocardial biopsy in myocarditis demonstrates a relatively distinctive diffuse lymphohistiocytic infiltration characterized by a predominant CD163-positive histiocytic infiltrate, with an associated CD8+ and PD-1+ T-lymphocytic infiltrate, some of which is granzyme B-positive [83]. In the acute setting, use of CMR for myocarditis diagnosis appears limited, as only one in five myocarditis cases demonstrates late gadolinium enhancement (LGE) when the CMR is performed at <4 days from myocarditis presentation; it may take some time for myocardial fibrosis to develop and accumulate before becoming detectable on CMR [78]. On the other hand, when CMR is performed later in the clinical course of myocarditis (≥4 days), nearly three out of four myocarditis patients have LGE [78]. Nevertheless, even among patients with myocarditis diagnosed with histopathology showing lymphocytic infiltration, only 38% have LGE and only 26% have an elevated T2-weighted STIR signal on CMR [78]. MACE does not necessarily associate with the presence of an LGE pattern or elevated T2-weighted STIR signal. Overall, as earlier treatment of myocarditis is associated with a lower rate of MACE, endomyocardial biopsy should still be considered among patients with a negative CMR, if there is a strong clinical suspicion for myocarditis.

Treatment

Myocarditis resulting from ICI cancer therapy should warrant rapid assessment, similar to acute coronary syndrome, as a delay is associated with a higher rate of MACE [63]. In suspected myocarditis cases, early initiation of corticosteroids in <24 hours from presentation has been associated with a 7% MACE rate, whereas corticosteroid initiation at >72 hours has associated with an 85% MACE rate [84]. There was an inverse relationship between initial dose of corticosteroids (measured in methylprednisolone equivalents) and the occurrence of MACE where <60 mg/day recipients experienced a 62% MACE rate, while 501–1000 mg/day recipients experienced a MACE rate of only 22% [84]. Overall, initiation time of corticosteroids appears to play an important role such that using a higher dose of corticosteroids may not overcome the late effect of delayed corticosteroids [84]. We favor treating suspected myocarditis cases, including those with pending endomyocardial histopathology results, with 1000 mg/day of methylprednisolone, which in our experience is associated with decreasing troponin levels and improvement in cardiomyopathy and tachybrady arrhythmias within 24 hours of corticosteroid initiation.

When needed, we utilize mechanical circulatory support, such as intra-aortic balloon pump or Impella, a micro-axial flow pump placed across the aortic valve, in myocarditis patients experiencing cardiogenic shock, with concurrent initiation of immunosuppressive therapy. Whether to start extracorporeal membrane oxygenation should involve shared decision-making among the providers and the patient or patient surrogates while keeping in mind long-term cancer-related prognosis.

We dose 1000 mg/day of methylprednisolone for 3–5 days [85], followed by prednisone taper starting at 1 mg/kg/day, provided troponin assays show a downward trend, and any complete heart block, ventricular arrhythmias, or cardiogenic shock has resolved [63]. Clinicians can also consider starting mycophenolate as a steroid-sparing agent to facilitate a more rapid taper off corticosteroids, although robust data on use of mycophenolate in this clinical context is lacking.

There is limited data on second-line immunosuppressive agents for patients refractory to corticosteroids with most case report-based data available for ATG therapy [75]. In a single-patient case report, the CTLA-4 agonist abatacept has been reported to be effective for steroid-refractory myocarditis [86]. However, cancer outcomes after CTLA-4 agonist therapy remain unknown. In another single-patient case report, alemtuzumab, which is an anti-CD52 monoclonal antibody, has also been shown to treat steroid-refractory myocarditis; the safety of alemtuzumab use in this population warrants further investigation [87]. There is paucity of non-case report-based data on the use of other therapies such as infliximab, intravenous immunoglobulin, and plasma exchange.

Conduction Disturbances

Arrhythmias are an increasingly recognized issue for cancer patients. Heart rhythm disturbances can be a consequence of various cancer therapeutics and can significantly impact optimal delivery of care. The majority of observed arrhythmias are supraventricular, particularly atrial fibrillation, and can lead to significant morbidity but are rarely life-threatening

[88]. If atrial fibrillation or other supraventricular tachycardia is accompanied by severe hypotension, then emergent cardioversion is necessary; however, most cases can be managed conservatively [89]. Less commonly observed arrhythmic complications include ventricular tachyarrhythmias and conduction disorders such as complete heart block. These can be either a direct consequence of the cancer therapy or a result of another cardiotoxicity such as cardiomyopathy or ischemia. Regardless, when these occur, expeditious intervention is necessary to avoid potentially serious and life-threatening consequences.

The risk of ventricular arrhythmias in cancer patients is primarily related to QT prolongation, which is frequently encountered in this population. The QT interval is an ECG measure of ventricular depolarization and repolarization, and significant prolongation is a marker of increased risk of *torsades de pointes* (TdP), a specific type of polymorphic ventricular tachycardia (VT) [90]. The likelihood of developing TdP increases with QT intervals greater than 500 milliseconds (ms) or with a change in the QT interval of more than 60 ms from baseline [91]. Among cancer patients, various factors contribute to QT prolongation. Specifically, electrolyte abnormalities such as hypokalemia and hypomagnesemia are well known to prolong the QT interval and lead to TdP, and these frequently occur secondary to cancer-associated nausea, vomiting, and diarrhea. Moreover, QT prolongation is more common in older individuals, women, as well as patients with underlying renal and cardiovascular disease [91].Additionally, various pharmaceuticals frequently prescribed to cancer patients have QT-prolonging potential which can be augmented in the setting of the aforementioned conditions. Specifically, certain antibiotics, antifungals, antidepressants, and anti-nausea medications are well known to increase the QT interval [91]. Additionally, various cancer therapeutics from traditional cytotoxic chemotherapy to targeted therapies are associated with QT prolongation [92]. Despite significant attention paid to the QT interval in oncologic drug development and monitoring, the actual risk of arrhythmia remains quite low. A study by MD Anderson evaluating patients enrolled in various phase 1 clinical trials reported a 20% incidence of QT prolongation with rates of TdP well below 1% [93]. Electrolyte repletion, avoidance of multiple QT-prolonging agents, and routine ECG monitoring are common strategies to mitigate the risk.

Among cytotoxic chemotherapeutics, QT prolongation is most frequently observed with arsenic trioxide, which is used primarily in the treatment of acute promyelocytic leukemia. In one study of over 3000 ECGs, 26% had a QT interval of more than 500 ms though no clinically significant arrhythmias were reported [94]. Implementation of aggressive risk mitigation strategies including electrolyte repletion and discontinuation of therapy when the QT interval is >500 ms, with resumption of the drug once the QT interval is <460 ms, has led to low TdP event rates [94]. Nevertheless, this drug carries a FDA black box warning for QT prolongation and sudden cardiac death [95].

QT interval prolongation is also an issue with certain targeted therapeutics including TKIs and cyclin-dependent kinase (CDK) 4/6 inhibitors. Among the TKIs, at least ten have standard or black box warnings for QT prolongation and sudden cardiac death. TKIs most commonly associated with QT prolongation include sunitinib, nilotinib, and vandetanib, with the latter two having an FDA black box warning. Sunitinib is a small molecule TKI used in the treatment of various solid tumors including renal cell carcinoma and gastrointestinal stromal tumors (GIST). There was a 2.3% incidence of QT prolongation greater than 500 ms with sunitinib though malignant arrhythmias occurred in less than 0.1% of treated patients [96]. Nilotinib is a second-generation BCR-ABL TKI used in the treatment of chronic myeloid leukemia. In the ENESTnd trial, a phase 3, randomized, open-label study, no patients developed a Fridericia-corrected QT interval of more than 500 ms [97]; however, sudden cardiac death occurred in 0.3% of patients [98]. Although preceding QT prolongation was not documented in any of these cases, the drug still carries a black box warning [98]. Vandetanib is a TKI used for medullary thyroid cancer also which carries a black block warning; however, QT interval prolongation is substantial (up to 18%) and arrhythmic complications have been observed [99]. Nevertheless, while a recent meta-analysis confirmed the QT-prolonging potential of these drugs, it was not predictive of TdP or other life-threating arrhythmias [100]. Finally, QT prolongation is also a significant cardiotoxicity of ribociclib, a CDK 4/6 inhibitor used to treat metastatic hormone receptor-positive, HER2-negative breast cancer. In the MONALEESA-2 trial, 3% of participants had an increase in their baseline QT interval by >60 ms, with 3.6% having an average QT interval of >480 ms [101]. Although no episodes of TdP have been definitely proven, it is recommended to avoid using ribociclib if the baseline QT interval is >450 ms and hold the drug if the QTc prolongs to a value >480 ms [102]. Interestingly, this does not appear to be a class-related effect as other CDK 4/6 inhibitors do not demonstrate similar QT-prolonging potential.

Several cancer therapeutics are directly arrhythmogenic, leading to malignant ventricular arrhythmias in the absence of other cardiovascular abnormalities or QT prolongation. Ibrutinib is a small molecule inhibitor of the Bruton's tyrosine kinase used to treat various B-cell malignancies. While ibrutinib is most associated with atrial arrhythmias [103], there is also an increased risk for ventricular arrhythmias with an incidence of 596 per 100,000 person years [104]. The mechanism of ibrutinib's arrhythmogenesis remains unclear; however, there is increased mortality in the setting of ibrutinib-associated arrhythmias [105].

Life-threatening ventricular arrhythmias can also occur as a consequence of another cardiotoxicity. They are frequent complication ICIs, which harness the body's immune system to target cancer cells. Ventricular arrhythmias most commonly occur in the setting of myocarditis; however, they can also occur in the absence of documented myocardial inflammation and may be the first manifestation of ICI cardiotoxicity [106]. Overall incidence of ICI-induced ventricular arrhythmias is reported at 27%, with an incidence of 7% in the setting of normal EF [107]. In addition, ventricular arrhythmias also occur in the setting of anthracycline-induced cardiomyopathy. Several studies have demonstrated rates of ventricular arrhythmias similar to other non-ischemic cardiomyopathy etiologies. In a study by Mazur and colleagues, incidence of non-sustained VT was 73.9%, with sustained VT or ventricular fibrillation (VF) at 30.4% [108]. In a related study, the incidence of non-sustained VT, sustained VT, or VF was reported at 44.4% [109]. Ventricular arrhythmias may also occur as a result of myocardial ischemia/infarction which can be seen in the setting of 5-fluorouracil (5-FU)-induced coronary vasospasm [110].

If patients develop hemodynamically unstable ventricular arrhythmias associated with cancer therapeutics, treatment should be initiated using standard advanced cardiac life support (ACLS) algorithms, with prompt CPR and defibrillation if the patient is unconscious and without pulse or cardiovascular perfusion [111]. If the drug is actively being delivered via infusion, as is the case with ICIs or 5-FU, the treatment should be immediately stopped. For patients experiencing TdP, electrolytes should be promptly repleted, with intravenous magnesium given regardless of plasma concentrations [111]. Cardiac pacing is also an option since the QT interval shortens at higher heart rates (generally greater than 100 beats per minute) [112]. For patients with chemotherapy-induced cardiomyopathy and persistent systolic dysfunction, implantable cardioverter-defibrillators (ICDs) can be considered depending on the patient's oncologist prognosis and overall goals of care [112]. In fact, the MADIT-CHIC study demonstrated significant improvement in EF and LV volume in patients with chemotherapy-induced cardiomyopathy (EF <35%) and concomitant left bundle branch block [112]. In general, future administration of the offending cancer therapeutic should be avoided in patients that have developed a life-threatening ventricular arrhythmia except in rare and individualized circumstances.

Bradyarrhythmias are associated with various cancer therapeutics including the taxanes and crizotinib, an ALK-inhibitor TKI for non-small lung cancer; however, they are generally asymptomatic and inconsequential [113, 114]. Rarely, severe symptomatic bradycardia or advanced conduction system disease including complete heart block can occur with certain treatments. High-degree atrioventricular block is a known manifestation of ICI cardiotoxicity [80]. In a large multicenter ICI myocarditis registry, complete heart block was part of the composite major adverse cardiac events that occurred in 46% of cases [63]. In fact, complete heart block is often the first indication of ICI myocarditis and can be fatal [80].

Treatment of advanced conduction disease and/or bradycardia first involves cessation of the offending agent. In the case of hemodynamic instability and/or serious symptoms, temporary transvenous pacing should be considered [115]. In many situations, recovery of conduction is possible, but if heart block persists more than 3–5 days, then a permanent pacemaker should be implanted [116]. In the case of myocarditis, there should be a low threshold to also implant an ICD if ventricular arrhythmias and left ventricular systolic dysfunction coexist with heart block [116].

Arrhythmic complications of cancer therapeutics are an emerging area of recognition and concern. In most cases, arrhythmias can be managed without significant sequelae. Rarely however, arrhythmias can present as life-threatening emergencies that require prompt medical attention. Specific cancer treatments can lead to sustained symptomatic ventricular tachyarrhythmias or advanced conduction system disease, often necessitating resuscitative efforts. In particular, various targeted therapies are associated with QT prolongation, which can lead to TdP, and certain treatments are directly arrhythmogenic to the ventricular myocardium. Advanced conduction system disease is most commonly associated with ICI myocarditis. Given the severity of these toxicities, improved screening and monitoring strategies must be developed to minimize patient risk while allowing them to continue receiving necessary and potentially life-saving cancer treatment.

Valvular Heart Disease

Therapeutic advances in chest radiotherapy have improved survival in patients with thoracic malignancy. As a result, patients are living long enough to unveil latent cardiac toxicity [117]. Although radiation-induced heart disease (RIHD) can manifest in a variety of pathologies, valvular disease imposes a high cardiovascular burden in cancer survivors and is associated with significant therapeutic challenges [117].

Pathophysiology

RIHD is largely attributed to direct endothelial damage caused by transient increases in oxidative stress and a resultant pro-inflammatory state. This leads to the upregulation of matrix metalloproteinase, adhesion molecules, cytokines, and collagen and is the hallmark of radiation-induced fibro-

sis [118]. Further to this, direct deposition of collagen on the heart valves leads to leaflet thickening and ultimately calcification resulting in regurgitation and/or stenosis [118]. The aortomitral curtain is classically affected and can mimic rheumatic heart disease, although is distinguished by the commissural fissure which is characteristically lost in rheumatic heart disease but not RIHD [119]. This cellular damage may be further confounded by the atherosclerotic contribution of traditional cardiac risk factors such as hyperlipidemia and smoking [118]. Additionally, the combination of anthracycline chemotherapy and mediastinal radiation as seen in common cancers such as breast, Hodgkin's lymphoma, and non-Hodgkin's lymphoma can further amplify RIHD [120].

Management of Valvular Heart Disease

Patients presenting with an acute valvular emergency require urgent stabilization, irrespective of their malignancy status. Symptoms and signs of acute valvular emergency may include dyspnea, tachycardia, pulmonary edema, and cardiogenic shock; patients can also present with angina or syncope, particularly with exercise. Accurate diagnosis of the underlying etiology of these findings may be confounded in oncologic patients with concomitant bleeding or anemia. Additionally, treatment-related factors including tumor lysis syndrome with hemodynamically significant fluid shifts and chemotherapy-related left ventricular dysfunction can contribute to acute decompensation of otherwise stable valvular disease [121].

Radiation-induced valvular disease may manifest as any valvular abnormality; however, left-sided valves are more commonly affected, most frequently the aortic valve [122]. Symptomatic severe aortic stenosis is associated with a high mortality without intervention, irrespective of cancer status [123]. This is particularly apparent in studies from the pre-transcatheter aortic valve replacement (TAVR) era which demonstrates a significant survival advantage in oncologic patients undergoing surgical aortic valve replacement (SAVR), regardless of cancer stage [124]. Despite this, current heart team risk assessment using the Society of Thoracic Surgeons (STS) score incorporates a history of cancer and chest radiation as covariates secondary to the greater burden of periprocedural complications in this group.

Modern Techniques

The innovation of TAVR has provided a platform to treat patients at increased surgical risk. Recent studies have demonstrated favorable results in patients with a history of chest irradiation undergoing TAVR with less adjusted 30-day mortality, less postoperative atrial fibrillation, and shorter hospitalization compared with SAVR, despite older age, higher STS score, and more baseline comorbidities [125–127]. However, patient selection for TAVR in the oncologic population must involve careful consideration of disease prognosis, both from the perspective of the oncologist and the cardiologist. The outcomes of patients with active cancer undergoing TAVR in a large registry study were recently described [128]. Although effective and safe in the short term, the use of TAVR in patients with active cancer was found to carry a worse intermediate prognosis compared with patients without cancer. This was largely attributed to cancer-related death and highlights the importance of individualized assessment regarding the appropriateness or futility of invasive valvular intervention.

Cardiovascular Imaging

With rapid increase in new therapeutics that leads to improved survival in cancer patients, we observe a concomitant increase in the morbidity and mortality attributed to their side effects. While cancer remains the second most common cause of death, worldwide, after heart disease, indeed, cardiovascular disease is the most common cause of death among cancer survivors. This may result from shared risk factors by cancer and CV disease, and/or due to toxic effects of therapeutics. As we begin to recognize trends and disentangle associations of cardiovascular outcomes with certain therapies, cardiovascular oncologic programs have relied on cardiac imaging for surveillance, early recognition, and management of treatment-related cardiotoxicities in cancer patients. Advanced imaging modalities can shed light onto pathophysiologic mechanisms and often recognize sub- or preclinical manifestations.

In this section, we will describe the role and utility of various imaging modalities in the evaluation of the cardiac emergencies discussed in this chapter, including myocardial dysfunction, ischemic heart disease, valvular heart disease, pericardial disease, myocarditis, amyloid, and non-ischemic vascular dysfunction. Importantly, we address the role of multimodality imaging in assessing various components of the cardiovascular system to paint a comprehensive snapshot of a patient's cardiovascular health. Indications for serial imaging and surveillance, in accordance with current guidelines, will also be discussed in the context of the underlying neoplasia and the presumed offending chemotherapy, immunotherapy, or radiation therapy. This section focuses on echocardiography, CMR, and cardiac CT. Yet it should be noted that *single-photon emission computed tomography* (*SPECT*) and positron emission tomography (PET) are also being explored in the preclinical and clinical setting for imaging patients in cardio-oncologic, particularly for myocardial perfusion and molecular imaging to detect subclinical cardiovascular dysfunction [129].

Echocardiogram

Widespread availability of echocardiography makes it the most utilized imaging modality for assessing myocardial dysfunction. Global longitudinal strain (GLS) is a particularly valuable tool in this setting. Guideline committees recommend performing echocardiogram with a GLS speckle-tracking technique at baseline, and at clinically reasonable intervals during treatment with anthracyclines, ICIs, and TKIs. Additionally, LVEF should be assessed at least annually after the end of treatment. Similarly, echocardiography for monitoring of LVEF and strain imaging are recommended at baseline and with every three cycles (or every 3 months) of trastuzumab, VEGF inhibitors, and every 6 months in the immediate post treatment period. Importantly, in emergent situations where patients undergoing treatment present with clinical symptoms of heart failure or those with a significant drop in LVEF on routine follow-up, echocardiography is a particularly useful tool to monitor the extent of damage and response to intervention. In addition to assessment of systolic function, echocardiogram is the modality of choice for evaluation of radiation-induced valvular heart disease and diastolic dysfunction commonly associated with cardiac remodeling [130, 131].

Initial changes in GLS often precede clinical manifestations of heart failure that would require emergent action. This provides an opportunity for the clinicians to assess and discuss the benefit-risk of continuing with the current cancer treatment plan. Such discussion may result in temporary or permanent change in the treatment plan, continuation of the plan with closer monitoring, or in some cases, the addition of cardioprotective agents to alter the progression of cardiac adverse effects.

Echocardiography with strain imaging should be strongly considered when suspicion of ICI toxicity exists. A recent study has shown that GLS is reduced in these cases, independently of the LVEF being reduced or preserved [82]. The definitions of "definite," "probable," or "possible" myocarditis all involve new wall motion abnormalities on echocardiogram, combined with a clinical syndrome consistent with myocarditis, biomarker evidence of myonecrosis, EKG evidence of myopericarditis, and/or negative angiography excluding obstructive coronary disease [132]. In cases where the pericardium is involved, echocardiography is, again, the first-line modality as it can assess for effusion and provide hemodynamic data suggestive of tamponade or constrictive physiology. Stress echocardiography is valuable for the assessment of wall motion abnormality secondary to ischemic cardiomyopathy in patients undergoing radiation or endocrine therapy in patients presenting with signs of stable or unstable coronary artery disease.

Cardiac Magnetic Resonance Imaging

In recent years, the use of CMR has grown exponentially due to its accurate evaluation of chamber quantification and function. Intracellular and interstitial myocardial tissue changes are more directly visualized with T2 and T1 mapping sequences. These changes, when detected early, can provide a valuable insight to the pathophysiologic mechanisms of cancer treatment associated-myocardial dysfunction. Early detection of edema and fibrosis, measured as extracellular volume fraction (ECV), and their surveillance during treatment could inform mitigation strategies to avoid progression to a cardiac emergency. As for now, guideline committees recommend CMR instead of echocardiogram only if echo is technically unfeasible, or where echo results are discrepant or suboptimal [130, 131].

In cases of new-onset heart failure where the etiology is unclear, CMR provides volumetric and mass data that can accurately assess fibrosis burden in the setting of patients undergoing radiation therapy or to confirm noninvasively a diagnosis of cardiac amyloidosis. Similarly, it may be used for hemodynamic assessment and evaluation of pericardial inflammation. Using T2-weighted imaging (representing free water and edema), one can assess for myocardial edema, to assess for myocarditis, which is useful in acute heart failure emergencies in those receiving ICI therapy [132]. Stress perfusion by CMR is an effective and noninvasive method of quantifying myocardial perfusion reserve when an ischemic insult is suspected. This imaging modality may be considered during evaluation of suspected TKI-related ischemia.

While no specific recommendations are provided for its use in these settings, CMR is a powerful diagnostic tool that may provide more granular data than traditional echocardiograms and may serve in lieu of more invasive methods (e.g., biopsy, angiography) in the right clinical setting.

Cardiac Computed Tomography

CT scans can also play a vital role in diagnosis and prevention of cardiovascular emergencies. Cardiac CT scans with contrast can identify stenosis to assist with ischemic cardiovascular disease diagnosis or intervention decisions or calcification to aid prevention planning. While coronary gating is important for assessing stenosis, calcification can be noted on chest CTs performed during lung cancer screening or follow-up. Aortic valve calcium score can also be assessed on CT, which can be particularly helpful when considering severity in the context of patients being considered for valve procedures such as TAVR. Pericardial calcification and effusion, as well as subepicardial delayed gadolinium enhancement suggestive of myocarditis, can also be assessed on

chest CT. Non-gated chest CTA is most often used to diagnose pulmonary embolism.

Cardio-Oncologic in the COVID-19 Era

The coronavirus disease 2019 (COVID-19) pandemic primarily spanning 2019–2020 posed unprecedented challenges for cardio-oncologic. The emergence of this new field of medicine coincided with a once-in-a-lifetime experience. Most clinicians and scientists will serve in at most one pandemic in their lifetimes. For some during this pandemic, their lifetimes were cut short. Healthcare workers across the globe sacrificed their lives, health, mental well-being, and time with their families in order to present daily at the frontlines and save lives. In cardio-oncologic, management decisions needed to be balanced between anticipated cardiovascular toxicities from cancer therapies and observed cardiotoxicities from COVID-19. Rapid implementation of innovative technologies related to telemedicine, artificial intelligence, and digital health paved the way for continued transformation in precision cardio-oncologic. Precision cardio-oncologic knows no bounds and has a tremendous potential to revolutionize our care for patients, using various "omics" in partnership with imaging, machine learning, computational simulation, *ex vivo* modeling, and mobile health [129, 133]. Combining biotechnological advances integrated in electronic health records with informatics tools for patient care in real time will likely herald a new era. The pandemic taught us how to raise the standard of emergency care, leading to a new outlook on care delivery.

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Superior Vena Cava Syndrome

22

Thomas C. Williamson, David E. Manthey, and Leslie R. Ellis

Case Study

A 65-year-old man with a 40-pack year smoking history presents to the emergency department complaining of shortness of breath and facial swelling that has acutely worsened over the last 24 hours. His vital signs are significant for O_2 saturation of 92% on 3 liters nasal cannula, respirations of 14/minute, blood pressure of 132/60, and heart rate of 100. Physical exam is significant for facial plethora, temporal wasting, decreased breath sounds over the right upper lung field, 1.5 cm left supraclavicular lymph node, ascites, and bilateral lower extremity edema. CT angiogram is significant for near complete occlusion of the superior vena cava without collateralization, a right upper lobe mass, and mediastinal and supraclavicular lymphadenopathy. The patient is admitted to the hospital and a bedside fine needle aspirate of the supraclavicular node is consistent with small cell carcinoma of lung origin. Further staging imaging, including MRI brain, does not reveal metastases. Treatment with chemotherapy (carboplatin/etoposide) is initiated.

Etiology/Epidemiology

Superior vena cava syndrome (SVCS) was first described by the Scottish physician William Hunter in 1757 in a case involving syphilitic infection of the aorta [1]. SVCS affects at least 15,000 people in the United States annually, occurring most commonly in patients between the ages 50 and 70 years [2]. Historically, the etiology of SVCS was predominantly infectious (syphilis, tuberculosis); however, at present, the majority of cases are due to malignancy. A review of 78 patients with SVC syndrome identified malignancy as the etiology in 60% of cases [3]. When malignancy is the cause, it is most commonly associated with non-small-cell lung cancer (50%), small-cell lung cancer (25%), lymphoma (10%), and metastatic lesions (10%), typically from breast cancer (Fig. 22.1). SVCS is actually found in a greater percentage of patients who have small-cell lung cancer (10%) versus non-small-cell lung cancer (less than 2%), but because of the greater incidence of non-small-cell lung cancer, the majority of cases of SVCS seen will be in this population [4]. Lymphomas associated with SVCS are overwhelmingly non-Hodgkin lymphomas, despite the fact that Hodgkin lymphoma typically presents with mediastinal lymphadenopathy. Common subtypes of non-Hodgkin lymphoma associated with SVCS include the diffuse large B-cell and lymphoblastic lymphoma subtypes. A type of lymphoma called primary mediastinal large B-cell lymphoma with sclerosis, although rarer, has a greater likelihood of being associated with SVCS when present, with up to 57% of patients having SVCS as presentation and over 80% having some radiographic evidence for the potential for SVCS [5, 6]. Obstruction of the superior vena cava in these situations is typically due to external compression from either the primary mass or an involved lymph node, although tumors less likely to be associated with SVCS can cause SVCS via intravascular extension and occlusion, such as intravascular large cell lymphoma or thymoma, among others [7, 8]. Approximately 2% of all cancer patients will develop some degree of SVCS [2, 9].

Surprisingly, up to 40% of the cases are now caused by indwelling lines secondary to an intrinsic thrombus associated with the line. In nonmalignant SVCS, it is estimated that intravascular devices account for up to 70% of cases [3]. This is felt to be due to not only compromised intraluminal laminar flow due to the presence of the indwelling line but also from alteration of the integrity of the vessel wall due to irritation of the endothelium by the catheter tip or wire lead [10]. However, only 1–3% of patients with central venous

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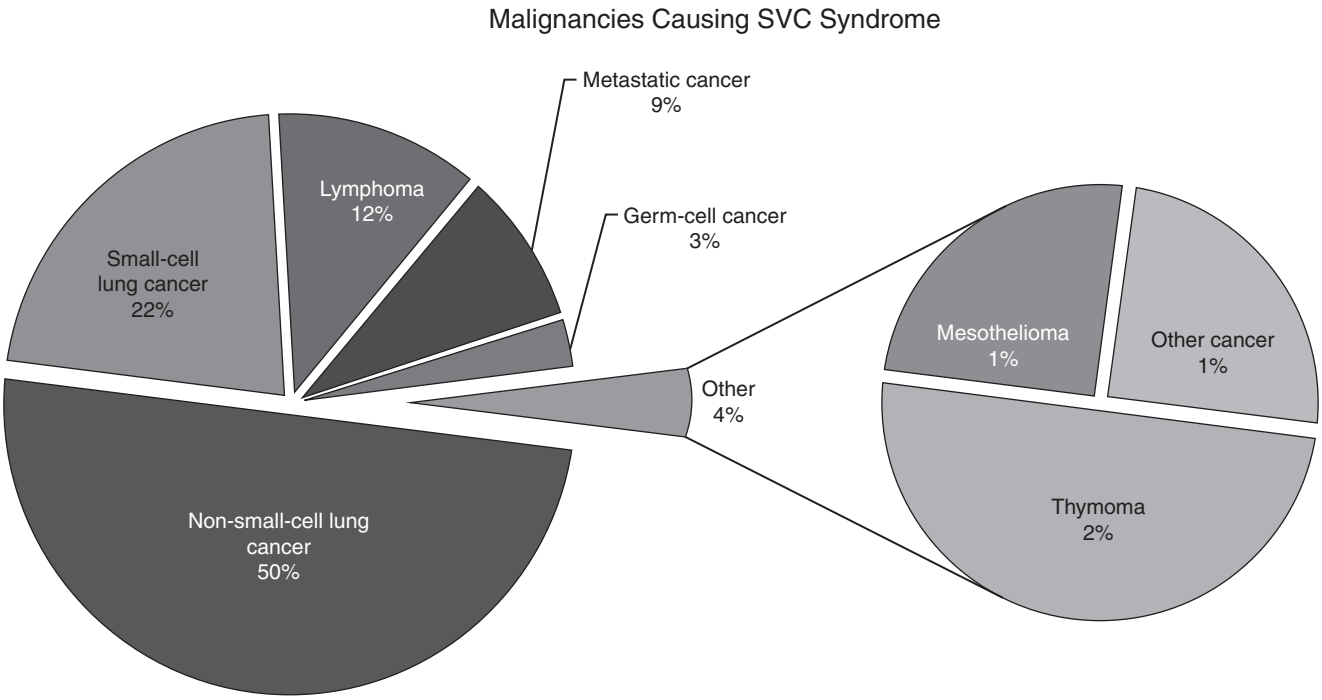

Fig. 22.1 Distribution of malignancies causing superior vena cava syndrome. (From McCurdy and Shanholtz [16], with permission from Wolters Kluwer Health and the Society of Critical Care Medicine)

catheters will become symptomatic [11]. This is commonly referred to as "benign" SVCS as it is not due to malignancy or alternatively because it is caused by intrinsic clot rather than external compression. A patient with benign SVCS is more often in the 30–40-year age range. Approximately 25% of pacemaker insertions are associated with obstruction or stenosis of the central venous system. It is reportedly less in patients with implanted pacemakers at an incidence of 0.2–3.3% [12]. Other nonmalignant causes of SVCS include mediastinal fibrosis, vascular diseases (atherosclerotic), infection (histoplasmosis, tuberculosis, syphilis, and actinomycosis), goiter, benign mediastinal tumors (cystic hygroma, thymoma, and teratoma), pericardial constriction, and nephritic syndrome. In pediatric patients, the cause of SVCS is most commonly iatrogenic secondary to indwelling central lines, ventriculoperitoneal shunts, or due to complications of cardiovascular surgery rather than caused by a cancer.

Anatomy

To fully understand the signs and symptoms of SVCS, the corresponding anatomy should be reviewed. The superior vena cava is 4–6 cm in length and 1.5–2 cm in width in an adult. It originates from the left and right innominate veins and terminates into the right atrium. The SVC does not contain any venous valves. The vein itself is thin walled and therefore easily compressible. It is surrounded by lymph nodes that may become enlarged and cause external compression. It is joined just above the right atrium by the azygos vein, which drains the veins from posterior aspect of the abdominal to chest cavities. The azygos vein can become an alternative drainage system for the upper extremity through collateral veins if it is not obstructed (Fig. 22.2). An obstruction of the SVC above the azygos vein, and therefore not involving the azygos vein, may present with less severe and more insidious onset of symptoms. Other potential sites for collateral development include the internal mammary veins, lateral thoracic veins, paraspinal veins, and esophageal veins, although the ability of these systems to fully compensate for SVC obstruction is more limited than the azygos vein system. The development of these collaterals usually occurs over a period of weeks; therefore, SVCS due to rapid tumor growth may not be associated with sufficient collateral development and symptoms may be more severe. When the vena cava is obstructed, the venous pressure in the cervical veins increases to 20–40 mmHg, significantly higher than the normal range of 2–10 mmHg [13]. Development of collaterals and the rapidity of the obstruction will affect the actual values.

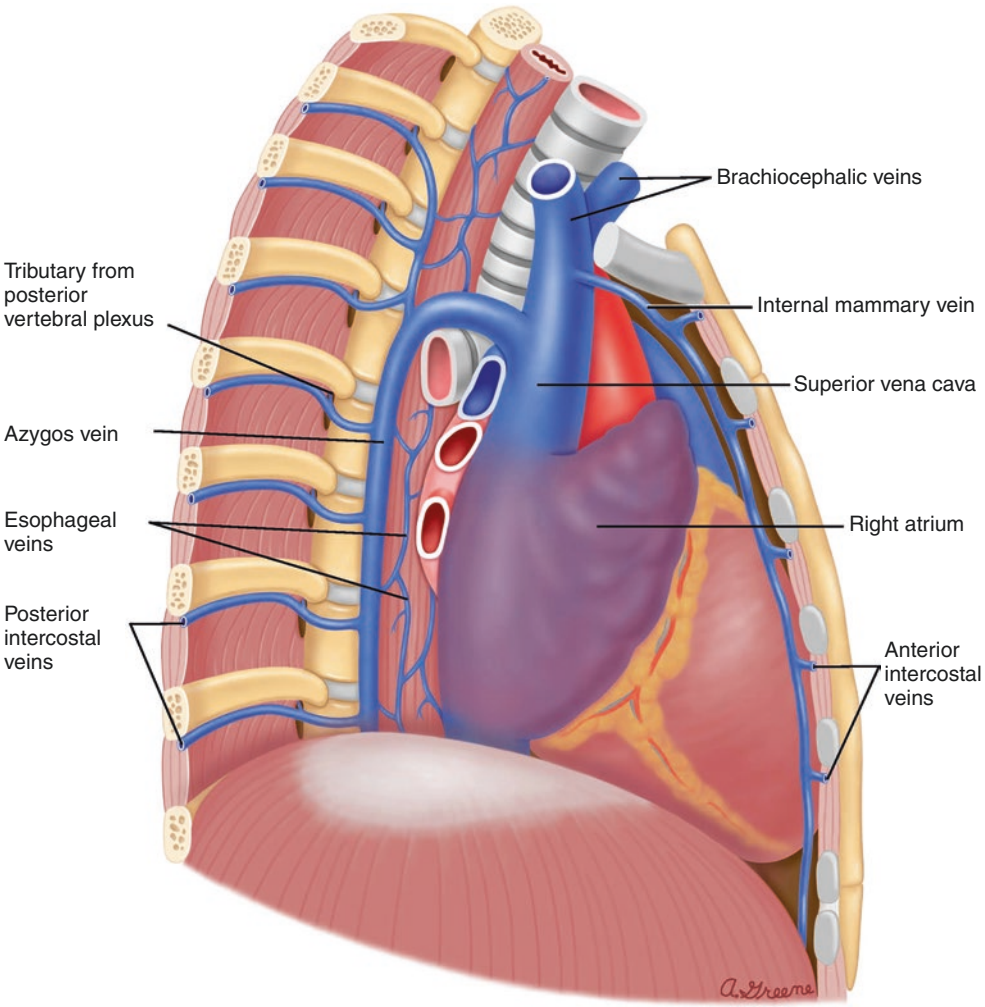

Fig. 22.2 Anatomy of the superior vena cava and veins of the mediastinum. (From Drews and Rabkin [14], with permission. Accessed on 27 July 2020. Copyright © 2020 UpToDate, Inc. For more information visit www.uptodate.com)

Clinical Features (Signs/Symptoms)

The clinical features of SVCS align with what you would expect to encounter due to obstruction of the major venous drainage of the head, neck, and upper extremities (Fig. 22.3 panel a). The most common sign of SVCS is facial edema (82%), which may be most noticeable in the morning after being in a recumbent position or with bending forward. Even in the presence of marked physical changes due to facial edema, this is rarely of clinical consequence [15]. Additional signs include distended neck veins (63%), distended chest veins (53%), arm edema (46%), and facial plethora, also referred to as a red ruddy complexion (20%) [16]. An interesting sign is the Pemberton sign, which is the exaggeration of the edema and flushing of the face due to the placement of the patient's arms over the head [17].

Most patients have symptoms for 2–4 weeks before a diagnosis is made. As discussed earlier, the development of collateral vessels may delay the onset of symptoms and signs. The most common symptoms of SVCS are cough (54%) and dyspnea (54%). The latter is commonly due to an associated pleural effusion and is seen more often in malignancy-associated SVCS. Additional symptoms include hoarseness (17%), syncope (10%), headaches (9%), and dizziness (6%). Stridor may occur in 4% of patients due to swelling around the trachea. Confusion (4%) and obtundation (2%) may also be present if cerebral edema is occurring but are unlikely to be the only complaint. Visual symptoms (2%) are also rarely encountered. It is important to note that improvement in these symptoms does not necessarily represent resolution of SVCS but instead may reflect the development of an adequate venous collateral system. Additionally, symptoms may not be due solely to SVCS but due to direct compression of additional structures by the primary or metastatic mass. This pearl is especially important when considering altered mental status or neurological findings, which may be due to increased venous pressure in the cranial vault or due to brain metastases from the primary tumor [18]. The

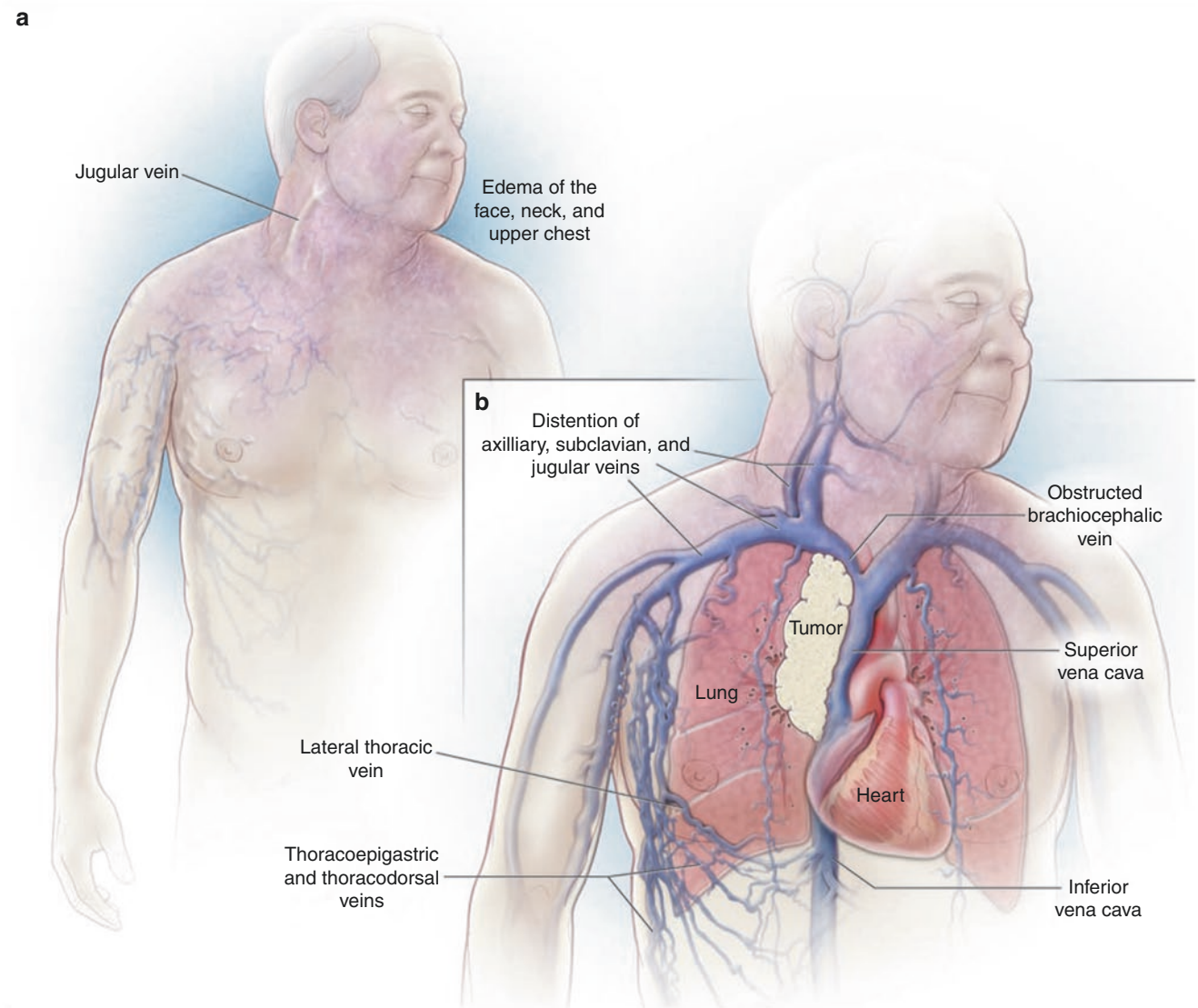

Fig. 22.3 Clinical findings in a patient with superior vena cava syndrome, including facial edema, plethora, jugular venous distention, and prominent superficial vascularity of the upper chest and neck, are shown in panel (**a**). The vascular anatomy of the upper chest, including the heart, superior vena cava, inferior vena cava, and subclavian vessels, is shown in panel (**b**). The tumor is shown compressing the superior vena cava. (From Wilson et al. [2]. ©2007 Massachusetts Medical Society, with permission)

most concerning signs and symptoms are those suggesting respiratory compromise or cerebral edema, as this may be life threatening. Because over 70% of malignancies associated with SVCS are either small-cell or non-small-cell lung cancer, an accurate history as to tobacco use is important. A thorough lymph node exam may identify palpable supraclavicular lymphadenopathy or multiple areas of lymphadenopathy, both of which have a high likelihood of being associated with malignancy [19]. Additionally, a thorough physical exam may identify targets that are easily amenable to tissue biopsy in order to establish a diagnosis, as illustrated in the case study.

Radiographic Evaluation

Although the diagnosis is suspected on a clinical basis, it is confirmed by radiologic studies. The chest radiograph (CXR) is abnormal in 84% of patients with SVCS, reflecting the malignancy that is causing the obstruction [2]. Findings on CXR include mediastinal widening (64%) and a superior mediastinal mass, 75% of which occur on the right side, consistent with SVC anatomy (Fig. 22.4). Pleural effusions are found in 25% of patients and, in older radiologic literature, are purported to be found mostly on the right side.

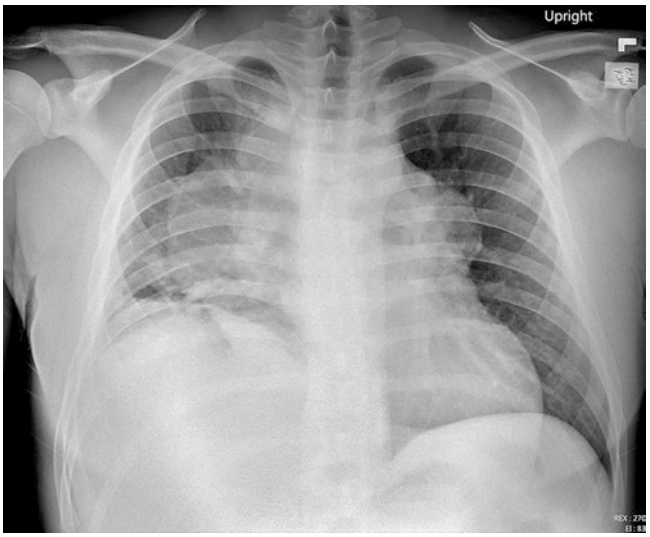

Fig. 22.4 Radiographic evidence of mediastinal mass (lymphoma) with right-sided pleural effusion

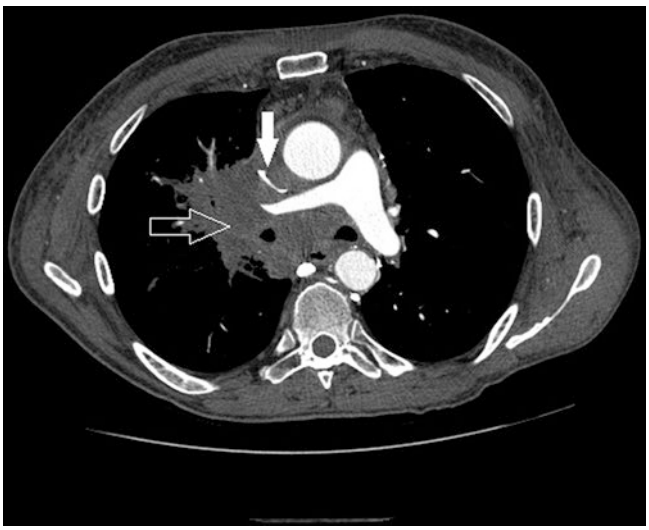

Fig. 22.6 Superior vena cava syndrome caused by lung cancer. *White open arrow* pointing to mass obliterating the right main stem bronchus. *White closed arrow* pointing to collapsed superior vena cava

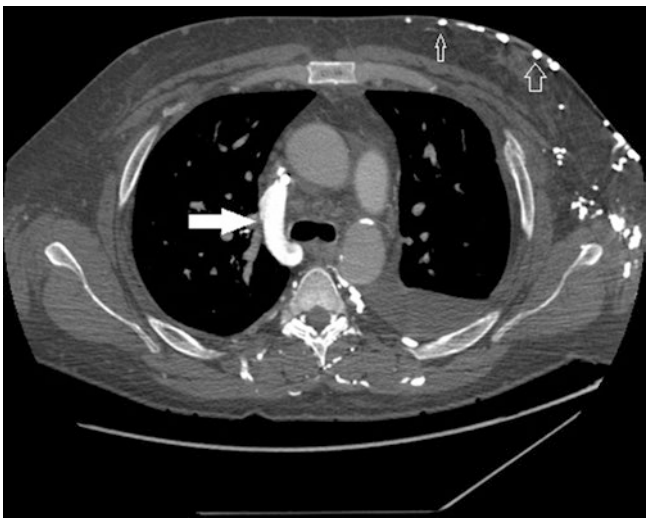

Fig. 22.5 Superior vena cava syndrome with blood returning via collaterals draining to the azygos vein. *White open arrows* pointing to collaterals. *White solid arrow* pointing to azygos vein

For definitive diagnosis, computed tomography (CT) of the chest with intravenous contrast is the modality of choice. CT angiography (CTA) can identify the location of the obstruction as above or below the azygos vein. At the same time, it will identify the development of collateral vessels (Fig. 22.5). It can differentiate between intrinsic clot and mass versus extrinsic compression of the superior vena cava with or without a superimposed thrombus [20] (Fig. 22.6). In addition, a chest CT may give information about structures such as the vocal cords/airway, as well as where best to perform a biopsy (via mediastinoscopy, bronchoscopy, or percutaneous fine needle aspirate). CTAs have sensitivities of 96% [21]. However, CT imaging and magnetic resonance angiography (MRA) both require the patient to lie flat, which may increase dyspnea and therefore cause movement artifact on images, making interpretation more difficult.

One epidemiologic study found pleural effusions on CT, which occurred in 70% of cases when associated with malignant causes and in only 58% of cases associated with benign causes [22]. Most effusions are small, with the majority filling less than 25% of the hemithorax. Contrary to the expected, pleural effusions occur on either side with equal incidence. The effusions, when sampled, were found to be either chylous in origin or exudative. This differs from the classic thinking that the fluid was transudative due to hydrostatic pressure differences. The chylous origin may be due to obstruction of the thoracic duct or due to impedance of lymphatic flow.

As indwelling devices are a common cause of SVCS, those patients presenting with unilateral arm swelling and an indwelling device will often undergo a Doppler ultrasound of the upper extremity to rule out a thrombus in the subclavian, axillary, and brachiocephalic veins. It is important to note, however, that the SVC cannot be directly imaged by Doppler ultrasound (due to its encasement by the ribs) and therefore additional imaging such as CT is required. Some texts suggest that patency of the SVC can be indirectly determined by normal waveforms in distal veins such as the subclavian or brachiocephalic, but there is no definitive evidence to back this approach. Transesophageal echocardiography would allow for imaging of the SVC and the right atrium but is more invasive.

Contrast venography can also diagnose SVCS, but it requires a significant load of iodinated contrast and radiation

exposure. Venous cannulation of the affected arm may be difficult as well, and if completely obstructed, limited visualization will occur. Finally, extrinsic compression versus internal clot cannot be distinguished. Venography is commonly done before stenting by interventional radiology and will provide information about the patency of the vena cava, as well as the extent of collateral circulation.

Magnetic resonance angiography (MRA) is also relatively sensitive (92–96%) and may be used in those patients with allergy to contrast dye. However, MRA carries the risk of gadolinium-induced nephrogenic systemic fibrosis in patients with renal failure. It provides much greater detailed imaging of the mediastinal structures and can be viewed in multiple planes. Disadvantages include cost and duration of scanning in a dyspneic patient.

Positron emission tomography (PET) scans, either with or without CT scans, are commonly used to assist in the staging of malignant disease both before and after treatment. However, the benefit to diagnosing SVCS with a PET scan is still dependent upon the CT portion of the scan. Specifically, a PET scan without a CT scan will have the ability to show a PET-avid mass in the area of the SVC but will not be able to provide a clear picture of SVC compression or obstruction. Similarly, a PET/CT, with the CT scan performed without IV contrast, will provide better images of the mediastinal area, but diagnosis of SVCS will still be limited. The only way to definitively diagnose SVCS with a PET scan would be to obtain a PET scan followed by a CT scan with IV contrast. Due to the increased costs associated with PET scans and the relative decreased availability, PET scans remain a method of staging prior to initiation of treatment as opposed to a fast or accurate way to diagnose a patient with SVCS.

Histologic Diagnosis

Malignancies remain the most common etiology of SVCS. Malignancy must be confirmed by a tissue diagnosis, although this does not necessarily require a biopsy of the mass that is causing the SVCS. An individualized approach is needed to decide whether less-invasive means can be utilized to obtain a tissue diagnosis before proceeding to mediastinoscopy. Less invasive means of obtaining tissue diagnosis, such as bronchoscopy, transthoracic needle aspiration, palpable lymph node needle aspiration, sputum cytology, or thoracentesis with pleural fluid cytology, are often sufficient for diagnosis. The ideal diagnostic approach is based on underlying patient factors such as ability to tolerate procedure(s), location of disease, and risk of biopsy. For example, if a patient has a palpable supraclavicular or axillary lymph node, needle aspiration biopsy would be preferred as there is high pretest probability and low complication rate. If minimally invasive testing is not diagnostic and a high suspicion for malignancy remains, a mediastinoscopy or mediastinotomy can provide a diagnosis in greater than 90% of the cases, with little increase in complications, as only 3% of patients developed significant hemorrhage with the procedure [23, 24]. Whenever lymphoma is on the differential, an excisional biopsy is preferred in order to allow the pathologist to determine tumor architecture and have sufficient tissue to perform immunohistochemical staining, both of which aid in an accurate diagnosis of the particular subtype of lymphoma. As will be discussed below, most treatments for SVCS are directed toward the causative malignancy, and thus tissue diagnosis is of utmost importance.

Treatment

Historically, treatment for SVCS consisted of emergent radiation, steroids, and diuretics. Importantly, SVCS is described in many textbooks as an oncologic emergency; however, few cases require emergent therapy [25]. In order to attempt to distinguish which patients with SVCS would require aggressive therapy, a proposed staging system has been developed [15]. This algorithm proposes a different treatment approach based on the severity of disease as graded (Table 22.1).

As seen in the treatment algorithm (Fig. 22.7), emergent treatment is indicated only if altered mental status, respiratory distress, or hemodynamic instability is present. The emergent treatment in these cases would be either thrombolytic for thrombus or stent placement for extrinsic compression and/or thrombus. It is important to note that the majority of patients will not present in extremis requiring emergent intervention, allowing for expedited evaluation of the underlying etiology. If not emergent, therapy is supportive or directed at the underlying cause.

Table 22.1 Grading of symptoms associated with SVCS

Grade	Definition	Estimated incidence (%)
0	Asymptomatic; radiographic evidence	10
1	Edema in head/neck, plethora	25
2	Functional impairment of voice, facial muscle by edema (dysphagia, cough, visual disturbance)	50
3	Mild/moderate cerebral edema Mild/moderate laryngeal edema Poor venous return with orthostatic syncope	10
4	Confusion, obtundation Stridor Significant hemodynamic compromise	5
5	Fatal	<1

From Yu et al. [15], with permission Elsevier

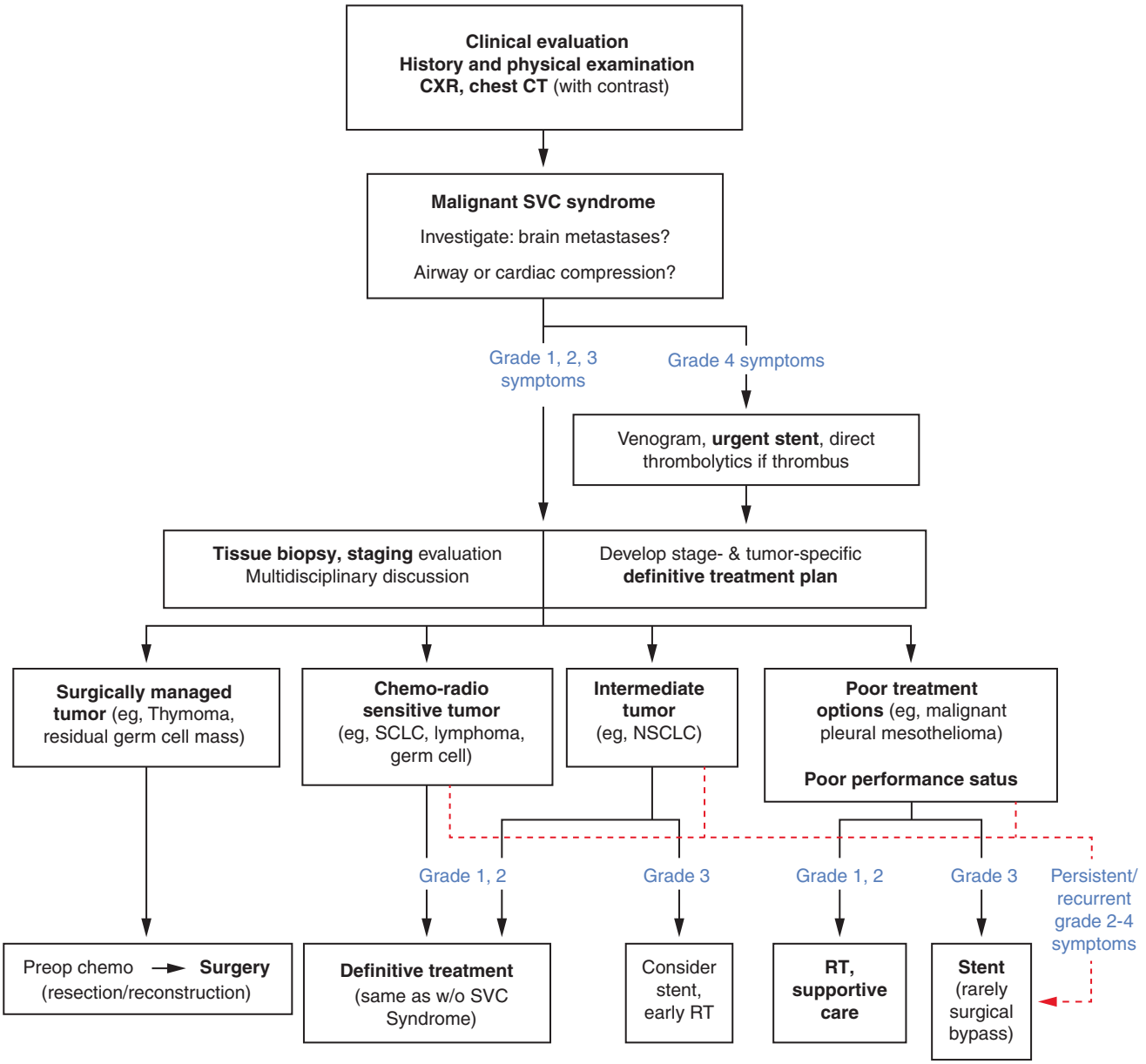

Fig. 22.7 Proposed algorithm for treatment of SVCS based on the severity of symptoms and etiology. (From Yu et al. [15], with permission Elsevier)

Supportive Therapy

In the recent past, glucocorticoids have been utilized based on case reports suggesting benefit. However, there is no good evidence to support their use outside of patients for whom lymphoma or thymoma is the cause of SVCS [4]. In a previously undiagnosed patient, this potential benefit should be weighed against the potential risk of eliminating a tissue diagnosis, especially in cases of suspected lymphoma. Diuretics have been used, again based on anecdotal evidence. Since the disease is based on limited flow return to the heart and not on volume overload, it makes little intrinsic sense to utilize diuretics.

Elevation of the head of the bed to theoretically decrease the hydrostatic pressure increase in the brain secondary to the elevated cervical venous pressures has been suggested and has little to no downside.

Treatment of Malignant Causes of SVCS

For patients with SVCS due to malignancy, treatment goals are twofold: (1) relieving the obstruction; and (2) treating the underlying malignancy. Initiation of treatment with chemotherapy and/or radiation therapy before a diagnosis is obtained not only exposes the patient to the side effects of the treatment without guarantee of response but also decreases the yield for an exact tissue diagnosis, with one study reporting only one of six patients (16.7%) having a histologic diagnosis obtained after chemoradiation therapy was initiated [26].

Chemotherapy

Chemotherapy is often the initial treatment of choice for SVCS if the tumor is felt to be chemotherapy sensitive. Small-cell lung cancer, non-Hodgkin lymphomas, and germ cell tumors are all considered chemosensitive, and even symptomatic patients with SVCS will have chemotherapy initiated first. This is in contrast to non-small-cell lung cancer, which traditionally is felt to be less chemosensitive and for whom radiation therapy is often the initial treatment of choice, with or without concurrent chemotherapy [27]. Multiple studies have shown that prompt initiation of chemotherapy in patients with small-cell lung cancer is effective (77% response rate) in alleviating SVCS symptoms within 1–2 weeks of treatment, although a small percentage of patients will experience recurrent obstructive symptoms (17%) [4, 28–32]. Similarly, for lymphomas, prompt initiation of treatment with chemotherapy is usually sufficient to prevent worsening of symptoms and alleviate obstruction (Fig. 22.8).

With greater understanding of the molecular pathways involved in malignancy, targeted therapies are more commonly employed either alone or in combination with cytotoxic chemotherapy. For example, the BRAF inhibitor, vemurafenib, has been shown to successfully treat SVCS in a patient with melanoma, with resolution of his symptoms by 72 hours [33]. In lung cancer, PD1 or PDL1 inhibitors (pembrolizumab, nivolumab, durvalumab, etc.) are most often given in conjunction with cytotoxic chemotherapy, although monotherapy could be considered in rare situations in which PD1 or PDL1 expression is high and/or the patient has poor functional status.

Radiotherapy

Again, almost 50% of malignancies causing SVCS are non-small-cell lung cancer. This tumor is more radiosensitive than chemosensitive; therefore, radiation therapy is the modality of choice for a patient presenting with symptomatic SVCS. In patients receiving radiation, either as monotherapy or in combination with chemotherapy, symptom improvement may begin as soon as 72 hours after initiation of treatment with the majority of responses occurring within 3 weeks. Relapse of SCVS after radiotherapy, chemotherapy, or combined therapy occurred in 16.7% of those with small-cell lung cancer and 20.8% with non-small-cell lung cancer [4]. It should be noted that radiation therapy can paradoxically worsen patients' symptoms with the development of edema associated with treatment. In the long term, radiation-

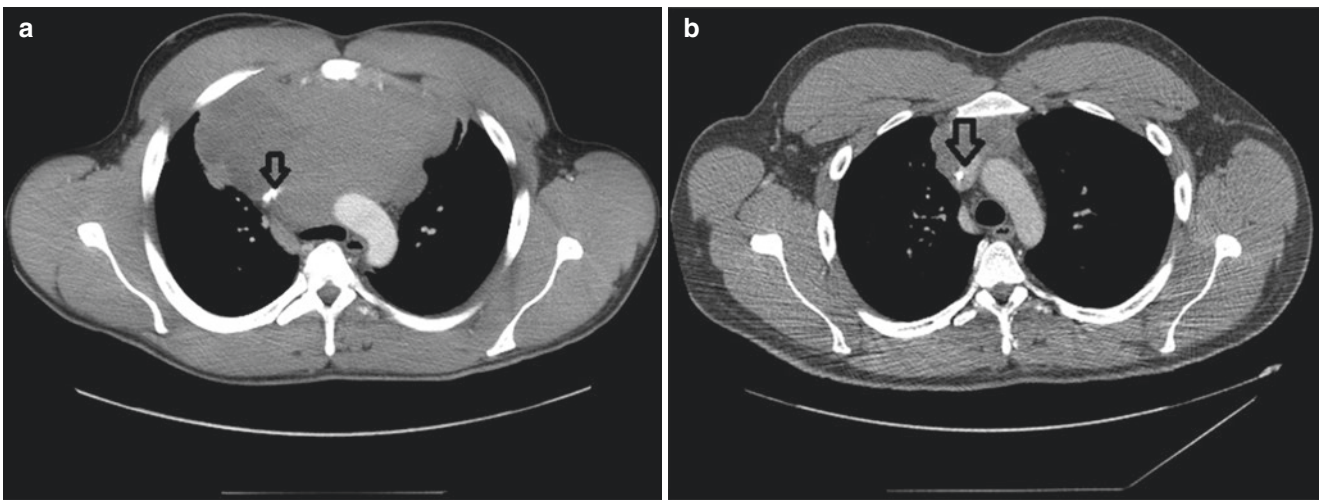

Fig. 22.8 (**a**) Superior vena cava syndrome caused by mediastinal tumor (lymphoma). *Black open arrow* pointing to collapsed vena cava with central line in place. (**b**) Same patient s/p induction chemotherapy with marked reduction in tumor burden. *Black open arrow* pointing to open vena cava with central line in place

induced fibrosis can result in recurrence of SVC obstruction, although the exact incidence is unknown [34].

However, it is difficult to discern how much of the improvement in symptoms is from the radiation therapy alone versus the development of a collateral vasculature sufficient to compensate for the obstruction. In an interesting study evaluating patients being treated with radiation therapy for SVCS, 85% of the patients reported improvement in symptoms, yet consecutive venograms showed that only 31% of patients had complete resolution of their SVC obstruction, and only 23% had partial resolution of the SVC obstruction. Evaluation during autopsy revealed even lower numbers, with only 24% of patients with either complete or partial resolution of the SVC obstruction [18].

Intravascular Therapy (Stents)

Stents are indicated as an emergent treatment or for cancer that is not responsive to treatment. Intravascular stents can provide symptomatic relief secondary to edema within 48–72 hours. However, one study found that only 17% of patients had complete relief with the stent, suggesting that the edema is multifactorial beyond the vena cava obstruction [35]. Tissue diagnosis will not be adversely affected by stent placement. Stents do not interfere with treatment of the cancer with either radio or chemotherapy and, most importantly, remain an additional treatment option for those patients who have recurrence of their SVCS after initially responding to either chemotherapy or radiation therapy [35].

Intravascular stents can be placed across the occlusive lesion, thus recanalizing the vein. Catheters are introduced from above via the internal jugular vein or below the diaphragm via the common femoral vein (Fig. 22.9). A femoral approach is beneficial in that it allows for assessment of the brachiocephalic veins and determination of the length of the SVC obstruction [36]. A wire is placed across the obstructive lesion. If recombinant tissue plasminogen activator is to be used, it is often delivered via a catheter with multiple side ports. Then a percutaneous balloon angioplasty is performed with a 10–16 mm angioplasty balloon. After the angioplasty, a stent is placed. The incidence of early re-intervention for thrombus in one study was 4%. Patency at 30 days was 96% [38].

In a study of patients with malignancy-associated SVCS, the treatment was clinically successful in 95% of cases (156 out of 164 patients) with an early mortality rate of 2.4%. Relapse occurred in 22% (36 patients), but re-stenting was successful in 75% of these patients. Recurrence was associated with occlusion, initial associated thrombosis, or the use of steel stents. Complications occurred more commonly if the stent was >16 mm in diameter [37]. Some have suggested using stents for indwelling catheters or primary treatment of benign SVCS [38].

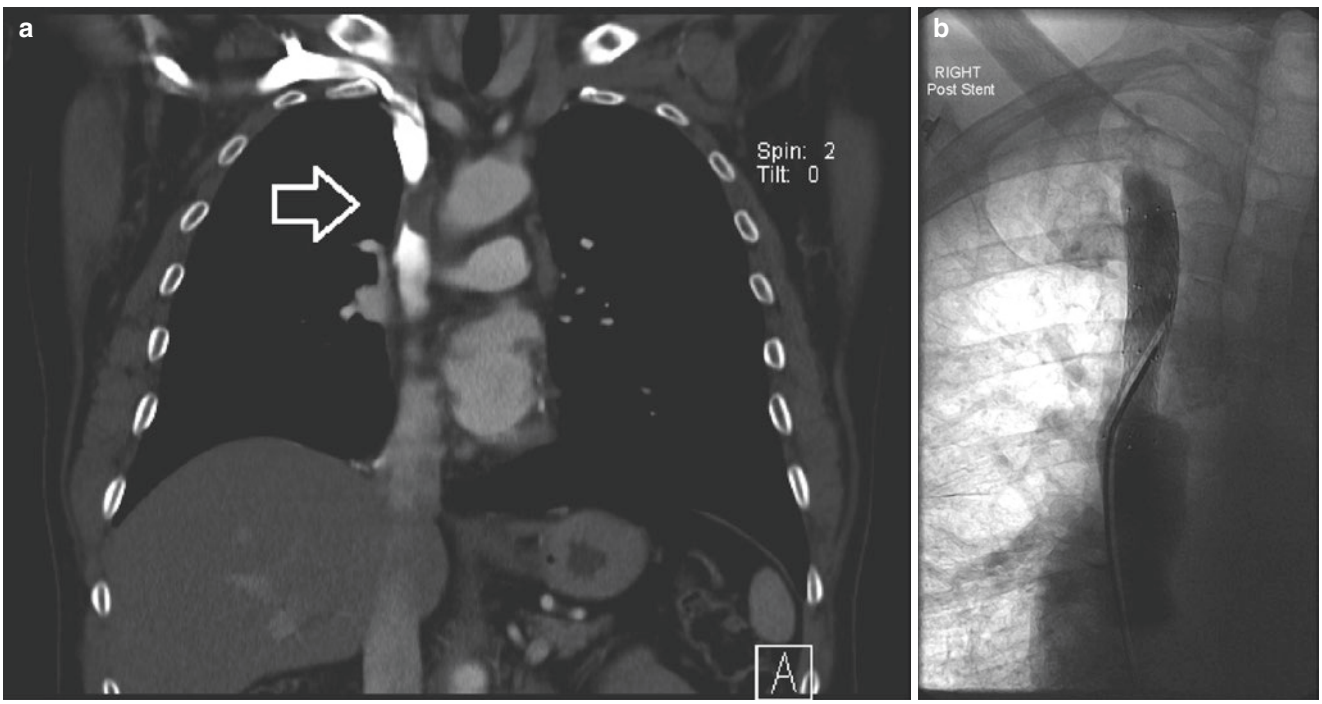

Fig. 22.9 (**a**) CT coronal view of superior vena cava syndrome. *White open arrow* indicates area of narrowing on contrasted study. (**b**) Deployment of a stent across the superior vena cava

Complications of stent placement include migration of the stent, hematoma at the site, perforation of the SVC, bleeding, infection, and pulmonary embolism. These have been reported in 3–7% of patients treated with stent placement [2].

Anticoagulation is often recommended after stent placement, but there are no evidence-based protocols to support this practice. Treatment is based upon the use of other stents and the treatment of other venous clotting. Typical practice is to use anticoagulation for 3–4 days post procedure with consideration for long-term anticoagulation based on an individualized assessment of risk factors for rethrombosis [36].

Treatment of Benign (Nonmalignant Causes) of SVCS

Medical treatment with steroids or diuretics has not been shown to be useful, especially in treating SVCS of benign origin. If an indwelling line is present, and the SVC was due to a clot, then anticoagulation is often utilized, although the effectiveness of this approach has not been shown either in the short- or long-term setting.

Thrombolytics

Patients who have developed SVCS due to intraluminal thrombus may benefit from thrombolysis, often in combination with stent placement. The use of thrombolytics (typically tissue plasminogen activator or urokinase) before stents are placed has been shown to decrease the length of blockage due to thrombus and therefore the number of stents placed [35, 39–43]. It is also felt that thrombolysis prior to stent placement decreases the burden of material that has the potential to embolize during stent placement. Adverse events, however, are increased as well when thrombolytics are used, including complications such as gastrointestinal hemorrhage, hemoptysis, and intracranial hemorrhage. This does have to be balanced with the relative success rate of thrombolysis, which has been reported to be as high as 88% [44]. Although typically thrombolysis occurs by pharmacological means, new advances in technology have provided additional methods of clot dissolution, primarily through the use of ultrasound-accelerated catheter-directed thrombolysis, which utilizes high-frequency sound waves in combination with tissue plasminogen activator [45]. This relatively new technology will require additional research to determine its efficacy relative to traditional chemical thrombolysis.

Prognosis

The outcomes of patients with malignant SVCS are directly related to the underlying malignancy and do not necessarily portend a lower overall survival compared to patients with similar tumor types who do not have SVCS [2]. Within the literature for small-cell lung cancer alone, studies have shown either no change or an improvement in overall survival for those patients who presented with SVCS when compared to patients who did not develop SVCS [28, 30–32, 46]. This may be due to patients with SVCS symptoms presenting to medical care earlier in the course of disease.

While many studies report the median life expectancy for a patient with SVCS as only 6 months, patients may survive over 2 years after treatment [15]. In some patients, treatment of the underlying malignant disease will result in cure of the disease and resolution of the SVCS.

In addition to the underlying etiology, poor prognostic factors for SVCS in patients with malignant cause include advanced age (>50), history of smoking, and use of steroids [47].

Recurrence (Durability of Treatment)

Almost 32% of patients with SVCS secondary to small-cell lung cancer, after treatment with chemotherapy, radiotherapy, or indeed both, have a recurrence of SVCS; however, these data are from 1983 and treatment advances may have improved this prognosis [29]. Relapse after placement of an SVC stent is approximately 11% (reported values of 9–20%). Most of these undergo a successful second stent placement, although a small percentage of patients will have recurrent obstructive symptoms (17%) [4, 28–32].

Palliative Care Discussions

As with any potentially life-threatening illness, palliative care considerations are a must. There are many definitions of palliative care, but most involve the concepts of preventing and minimizing suffering, optimizing one's quality of life, and aligning healthcare with patient goals and values. Many organizations, including the Institute of Medicine and the World Health Organization, recognize that palliative care specialists are integral to superior cancer care [48]. One widely quoted study identified an improved quality of life for patients with metastatic non-small-cell lung cancer who received early palliative care interventions while also receiving standard oncologic care [49]. The American Society of Clinical Oncologic clinic practice guidelines also recom-

mends involving palliative care specialists early in the disease course of patients with advanced cancer, in combination with chemotherapy and/or radiation therapy [50].

Many have used the concept of estimated life expectancy as a surrogate marker for when to more fully involve the palliative care team in a patient's care. In fact, the National Comprehensive Cancer Network's Guidelines for Palliative Care references a life expectancy of less than 6 months as a trigger to more actively engage palliative care, for which SVCS is one indicator [51]. However, additional factors must be taken into account, including the underlying malignancy, the patient's performance status, and patient goals of care. It is crucial that an oncologic specialist be involved in the conversations with the patient and other members of the healthcare team in order to provide an overall perspective of the disease course and potential outcomes.

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Pulmonary

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Case Study

A 73-year-old male with a remote history of smoking presented with complaints of worsening shortness of breath and dry cough. His imaging studies showed a large right pleural effusion, and a PET scan revealed extensive pleural hypermetabolism throughout the right hemithorax, suspicious for malignancy. Bronchoscopy and transbronchial needle aspiration were nondiagnostic. Pathological results of a pleural biopsy and pleural fluid were positive for Ber-EP4, MOC31, p53, and CK7 consistent with adenocarcinoma with lung primary. The patient was treated with one cycle of combination chemotherapy following which immunohistochemical staining indicated that 70% of the patient's tumor cells expressed PD-L1. The patient began a 3-week cycle of pembrolizumab. Initially, pembrolizumab was tolerated fairly well, but after completing four cycles of single-agent therapy the patient developed increasing dyspnea and CT chest showed patchy areas of ground-glass opacity throughout both lungs. Based on these imaging findings, the clinical course, as well as negative results of cultures and viral antibody tests, the patient was diagnosed with pembrolizumab-induced pneumonitis. Thereafter, immune checkpoint inhibitor was held and prednisone 40 mg per day with a slow taper begun. This regimen resulted in the regression of both the pulmonary opacities and symptoms.

Introduction

The worldwide surveillance of cancer survival during a 15-year period (2000–2014) was recently reported from 71 countries, including data on 18 cancer types. While cancer incidence is increasing, survival trends are reported to be increasing, even for some of the more lethal cancers [1]. This is directly linked to an aging population, improved diagnostics and screening tools for cancer, high population awareness, and more advanced therapeutic options. The incidence rate of new cancer cases in the United States is 436 per 100,000 population [2]. In 2019, there were an estimated 1.7 million new cancer cases diagnosed and 606,880 cancer deaths in the United States [2]. Intensive chemotherapy regimens and the use of new and more targeted therapeutic drugs have resulted in higher cancer cure rates. However, the treatment often leads to repeated invasive procedures, drug-related organ toxicities, and increased susceptibility to infection. As a consequence, emergency physicians and intensivists are increasingly managing cancer patients presenting with single- or multi-organ dysfunction. Pulmonary complications include respiratory failure, including acute respiratory distress syndrome (ARDS); pleural diseases (such as pleural effusion or pneumothorax); chemotherapy or radiation-induced pulmonary toxicity; hemoptysis; and pulmonary embolism.

Respiratory Failure, ARDS, and Ventilator Management

Respiratory Failure

Acute respiratory failure (ARF) is common in cancer patients, occurring in up to 50% of hematological malignancies and 15% of solid tumors or solid organ transplantation. It is associated with high mortality rate. Risk factors include invasive mechanical ventilation, organ dysfunction, advanced age, poor performance status, delayed intensive care unit admission, and invasive fungal infection [3]. Etiologies of respiratory failure in cancer patients are numerous. The most frequent etiologies include pneumonia, cardiogenic pulmonary edema, ARDS, chemotherapy or radiation-induced lung injury, pneumothorax and bronchopleural fistula, large pleural effusions, hemoptysis, and thrombotic/nonthrombotic embolus [4–6].

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Acute Respiratory Distress Syndrome (ARDS)

ARDS represents an acute and diffuse inflammatory lung injury. It leads to increased pulmonary vascular permeability, acute inflammation of the alveolar walls, and diffuse alveolar damage [3, 7]. Clinical hallmarks of ARDS are hypoxemia and bilateral radiographic opacities in the absence of heart failure. The hypoxemia is profound as defined by a ratio of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) of 300 or less. ARDS is further subdivided into mild (300–201 ratio), moderate (200–100 ratio), and severe (≤100 ratio) [8].

ARDS in patients with malignancies is not well studied, as these patients are often excluded from ARDS trials; however, a few studies are available [9, 10]. ARDS incidence is reported around 12% in all cancer patients in the ICU and 18% among those on mechanical ventilation. ARDS is more common in hematologic malignancies. Higher mortality was noted overall in retrospective assessment of ARDS network trials and was attributed to a more severe presentation and advanced age [11–13]. The mortality of cancer patients with ARDS in these trials was 54% compared to 24% among non-cancer patients [13]. In a more recent prospective study [10], the main factors associated with higher severity and mortality were the duration of mechanical ventilation and ICU stay prior to ARDS onset. Later onset was associated with higher mortality. Other risk factors included excessive positive fluid balance before ARDS onset and acute kidney injury. The presence of neutropenia is also an important contributing factor, whether a manifestation of the underlying cancer or secondary to chemotherapy. The course of ARDS in patients with neutropenia was different from that of the general population. In general, the outcome of ARDS is determined in the first 10 days, by which time half of the patients either have died or weaned off treatments. In patients with neutropenia, more than 85% of ICU survivors were still hospitalized after 10 days [14]. One recent study evaluated the various etiologies of ARDS in patients with malignancies; infectious etiologies were found in almost 90% of patients [15, 16].

In the same study [15], noninvasive positive-pressure ventilation (NIPPV) was used in more than a third of cancer patients with ARDS. Ultimately, the majority (71%) of patients on NIPPV required endotracheal intubation in correlation with severity of ARDS. Failure of NIPPV ventilation was associated with worse outcome. This study also examined potential prognostic indicators and found that two factors are associated with lower hospital mortality: solid tumor and primary ARDS (caused by direct lung insult, including infectious or noninfectious causes). Factors associated with higher mortality are allogenic bone marrow transplant, higher admission Sequential Organ Failure Assessment scores (SOFA) [17], presence of invasive fungal infection, and failure of NIPPV [4, 13].

Ventilator Management

Early recognition in the emergency department (ED) and initiation of supportive therapy, including mechanical ventilation, are mainstays in the management of ARDS patients.

ED length of stay for patients requiring admission to intensive care units has increased gradually in recent years [18]. Mechanical ventilation is an integral part of critical care and mechanically ventilated patients are commonly managed and monitored by emergency physicians. With the increasing demand for ED care as well as ICU beds [19], emergency physicians are expected to manage many patients on mechanical ventilation for prolonged periods of time. When invasive mechanical ventilation is initiated and managed in the ED, the emergency physician should have an understanding of open-lung ventilation and associated low tidal volume ventilation (LTVV) or lung-protective positive-pressure ventilation.

NIPPV delivered to selected patients obviates the need for an endotracheal tube. The ventilator is connected to the patient via a facemask. The mask is attached firmly to the patient's face using straps in order to prevent air leak. Most clinicians prefer the use of invasive intermittent positive-pressure ventilation (IPPV) over NIPPV in patients with ARDS considering the potential for hypoxemia to worsen in these patients and the risk for rapid deterioration. Other non-invasive ventilation strategies include high-flow nasal cannula (HFNC) oxygen therapy that delivers a high flow of heated and humidified gas. In a recent post hoc analysis including 82 immunocompromised patients, those treated with HFNC alone had a lower intubation rate than the NIPPV group (31% with HFNC vs. 65% with NIPPV). Similarly, the mortality rate at day 90 was lower with HFNC compared to NIPPV [20]. These differences were not observed between HFNC and the standard oxygen group. A prospective randomized study evaluated the early use of NIPPV versus high concentration of oxygen in a less severe group of patients with mild ARDS [21]. Despite a historical high rate of intubation in patients with ARDS initiated on NIPPV, this study showed a significant decrease in the respiratory rate, improved PaO_2/FiO_2 ratio, and lower incidence of subsequent organ failure. However, this study had a very selective young group of patients who were able to tolerate and cooperate with this mode of ventilation.

When using IPPV, it is very important to consider the following issues: (a) alveolar involvement in ARDS is heterogeneous; and (b) damage caused by adjustments in ventilation to maintain adequate blood gases may result in delayed additive iatrogenic lung injury. Therefore, LTVV (low tidal volume ventilation) is the preferred mode of ventilation for patients with ARDS. The rationale for this mode is that overdistension of the alveoli is a major reason for ventilator-induced lung

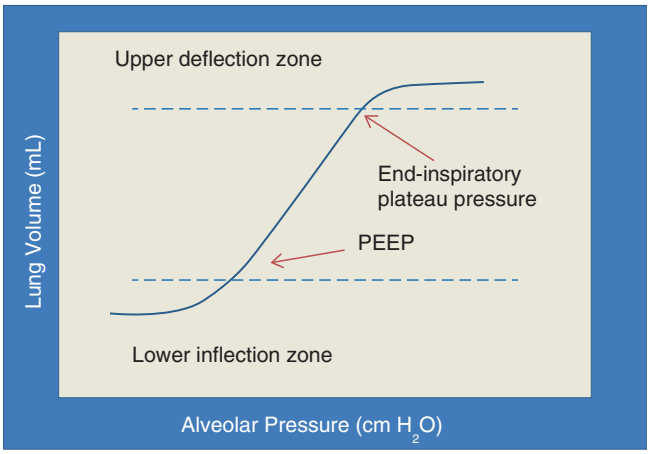

Fig. 23.1 The inspiration limb of a pressure–volume curve in an ARDS patient without PEEP application. Initial pressure application produces very little lung inflation as the pressure is applied against wet boggy lung. As lung begins to inflate, compliance improves and the curve assumes a steeper slope. As tidal volumes become too large for a lung that is questionable for ventilation (overinflation), the curve flattens. Low tidal volume strategy in ARDS should target avoiding moving into the flattening portion of curve (upper deflection zone, *upper arrow*). The goal of PEEP application is to avoid lung collapse at end inspiration and a repeated cycle of lung collapse and reopening with each delivered ventilation breath (with production of shear force injury or atelectrauma). Therefore, optimal PEEP would be applied at the lower end of the upslope of the curve (lower arrow, lower inflation point)

Table 23.1 ARDSnet PEEP table

Lower PEEP/higher FiO_2								
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
FiO_2	0.7	0.8	0.9	0.9	0.9	1.0		
PEEP	14	14	14	16	18	18–24		
Higher PEEP/lower FiO_2								
FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16
$FFiO_2$	0.5	0.5–0.8	0.8	0.9	1.0	1.0		
PEEP	18	20	22	22	22	24		

From NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary. http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf

Use a minimum PEEP of 5 cmH_2O. Consider use of incremental FiO_2/PEEP combinations such as shown below to achieve goal. Consider the higher PEEP table in the presence of more severe hypoxemia

PEEP Positive end-expiratory pressure, *FiO_2* Fraction of inspired oxygen

injury (Fig. 23.1). The majority of evidence suggests that LTVV improves mortality as well as other meaningful outcomes in patients with ARDS. The multicenter ARMA trial [22] compared LTVV (initial tidal volume 6 ml/kg predicted body weight, PBW) versus conventional ventilation (initial tidal volume 12 ml/kg/PBW). The benefits of LTVV were lower mortality rates (31 vs. 40%) and more ventilator-free days (12 vs. 10 days). As expected, LTVV may be associated with hypercapnia, which is generally well tolerated and may be associated with beneficial effects not directly related to LTVV [23, 24]. In permissive hypercapnia, the accepted and managed rise of $PaCO_2$ and subsequent acidosis increases arterial and tissue oxygenation by a right shift of the oxygen–hemoglobin dissociation curve and possibly by increasing cardiac output and circulating catecholamines. Hypercapnic acidosis reduces cyclic mechanical stretch-induced nuclear factor-κB activation, reduces interleukin-8 production, and decreases epithelial injury and cell death compared to normocapnia [24, 25]. However, the rise of $PaCO_2$ should occur gradually. Rapid rise should be avoided as the negative effects may exceed the beneficial ones (increased heart rate/blood pressure, arrhythmias, and pulmonary vasoconstriction/worsening hypoxemia). A typical approach for enacting a low tidal volume strategy in ARDS is as follows: (a) set tidal volume initially to 8 ml/kg/PBW; (b) titrate down to 7 and then 6 ml/kg/ PBW; (c) measure the airway plateau pressure (Pplat), if ≤30 cmH_2O, no other adjustment is required; and (d) if Pplat is >30 cmH_2O, then further decrease the tidal volume to as low as 4 ml/kg/PBW to achieve target. Higher Pplat may be allowed in the presence of obesity or anasarca ng volume (mL)

Open-lung ventilation represents the addition of positive end-expiratory pressure (PEEP) to the LTVV strategy, targeting to prevent collapse of edematous lung at end expiration. PEEP is believed to maximize alveolar recruitment and prevent cyclic atelectasis. According to several meta-analyses, the use of open-lung ventilation is associated with improved oxygenation; however, the effect on mortality has not been well established. The ARMA trial used a type of open-lung strategy in both arms, increasing PEEP levels with increasing severity of hypoxemia. Open-lung strategies have repeatedly shown improved oxygenation and perhaps more importantly, improved lung compliance. The titration of PEEP is typically based on oxygenation deficit or pressure–volume curves (see discussion below). When guided by oxygenation, start with the lowest PEEP possible to maintain an adequate PaO_2 of 55–80 mmHg with a FiO_2 of less than 60% and then titrate PEEP according to the ARDS net PEEP/FiO_2 protocol (Table 23.1) (http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf). When pressure–volume curves are used, it is important to calculate lung compliance and use a PEEP level that moves the end-expiratory P/V point onto the steep part of the pressure–volume curve (see Fig. 23.1).

One additional, nonventilation-related strategy is worthy of mention in the early management of ARDS patients, that is, the use of neuromuscular blockade. There is some evidence that early use of neuromuscular blockade agents in patients with ARDS is associated with better outcomes, including mortality [26, 27]. The recent Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial involved patients with ARDS who were treated with a strategy involving a high PEEP and who showed no signifi-

cant difference in mortality at 90 days between the cisatracurium group and the control group [28]. This finding is contrary to the results of the *ARDS et Curarisation Systématique* (ACURASYS) trial published in 2010, in which the adjusted 90-day mortality was lower in the cisatracurium group than in the placebo group [20, 26, 27, 29].

In the paralyzed patient, both the Pplat, as an estimate of end-inspiratory pressure, and the pleural pressure Ppl are positive; therefore, the TP pressure estimate is Pplat − Ppl. In the spontaneous breathing patient, the pleural pressure may be negative at end inspiration, and this negative pressure will increase transpulmonary pressure with the delivery of the same tidal volume. Paralysis, by eliminating inspiratory effort, would be expected to decrease TP pressure in the presence of overinflation, thereby decreasing the risk of ventilator-induced lung injury.

Summary

Acute respiratory failure and ARDS are common in patients with malignancies. Infectious etiologies are most common. Early recognition and intervention are crucial and should be initiated in the ED upon presentation. A trial of NIPPV/HFNC is acceptable initially in stable and cooperative patients. Lung-protective and open-lung ventilation strategies are keys to improve outcomes and survival. Given the limited treatment options for ARDS, and the early onset after admission, measures to prevent onset and mitigate severity should be instituted in the ED.

Pneumothorax and Pleural Effusion

Pleural manifestations are not uncommon in patients with malignancies. The pleura is often a metastasis site from local or distant cancers, presenting more commonly as pleural effusions rather than solid masses. Also, the pleura can be involved with spontaneous or iatrogenic pneumothoraces in patients with malignancies.

Pneumothorax

Definitions, Etiologies, and Diagnostic Modalities

Pneumothorax refers to the presence of air in the pleural space. The classification of pneumothorax includes spontaneous, traumatic, or iatrogenic. Spontaneous pneumothorax occurs without obvious cause, either primary without evidence of underlying lung disease, or secondary with apparent underlying lung disease, often COPD. Traumatic pneumothorax occurs after blunt or penetrating trauma to the chest. Iatrogenic pneumothorax occurs after a diagnostic or therapeutic intervention, such as transthoracic lung biopsy, central line placement, or barotrauma, due to mechanical ventilation. The incidence of pneumothorax in patients receiving mechanical ventilation ranges between 7% and 14% [30]. Patients with acute lung injury or ARDS are at increased risk.

Clinical manifestations are widely variable, ranging from asymptomatic to respiratory failure to prolonged bronchopleural fistulas (BPFs). Prompt diagnosis and management are crucial especially in symptomatic patients with underlying lung diseases or critically ill patients requiring mechanical ventilation.

Sometimes found incidentally on routine chest imaging, the presence of a pneumothorax is clinically suspected in the appropriate clinical setting. A small pneumothorax can be asymptomatic and self-limited, whereas a large pneumothorax can cause hypoventilation, hypoxemia, and/or hemodynamic instability.

Tension pneumothorax represents a surgical emergency and requires emergent intervention. It may lead to respiratory failure requiring mechanical ventilation. It may also complicate preexisting respiratory failure on positive-pressure ventilation.

In intubated and sedated patients, a pneumothorax should be suspected with sudden and unexplained worsening respiratory failure, increased oxygen requirements, hemodynamic instability, and a sudden rise in peak and plateau pressures. It is frequently diagnosed based on clinical presentation, risk factors, and physical exam (not by imaging) and should be treated by immediate emergent decompression in hemodynamically unstable patients. However, the increasing availability of bedside ultrasonography has made emergent imaging confirmation of pneumothoraces possible prior to emergent decompression.

The current first-line imaging modality used to identify a pneumothorax is chest radiography, although bedside ultrasonography has great potential to compete as the diagnostic method of choice in the future. The typical finding is displacement of the white visceral pleural line from the chest wall on an upright chest radiograph. The underlying lung parenchyma should be examined for the presence of lung disease that might suggest a cause for the pneumothorax. In bedridden or ICU patients, care should be exercised in order to differentiate the visceral pleural line from skin folds. Skin folds frequently extend beyond the rib cage; blood vessels and lung parenchyma often extend beyond the skin fold. Their attenuation profile is also different, forming a negative black Mach band instead of the white visceral pleural line (Fig. 23.2).

Computed tomography (CT) diagnosis is best utilized for complicated or unclear situations. CT scans are more accurate in determining size of pneumothorax when compared to chest radiography [31].

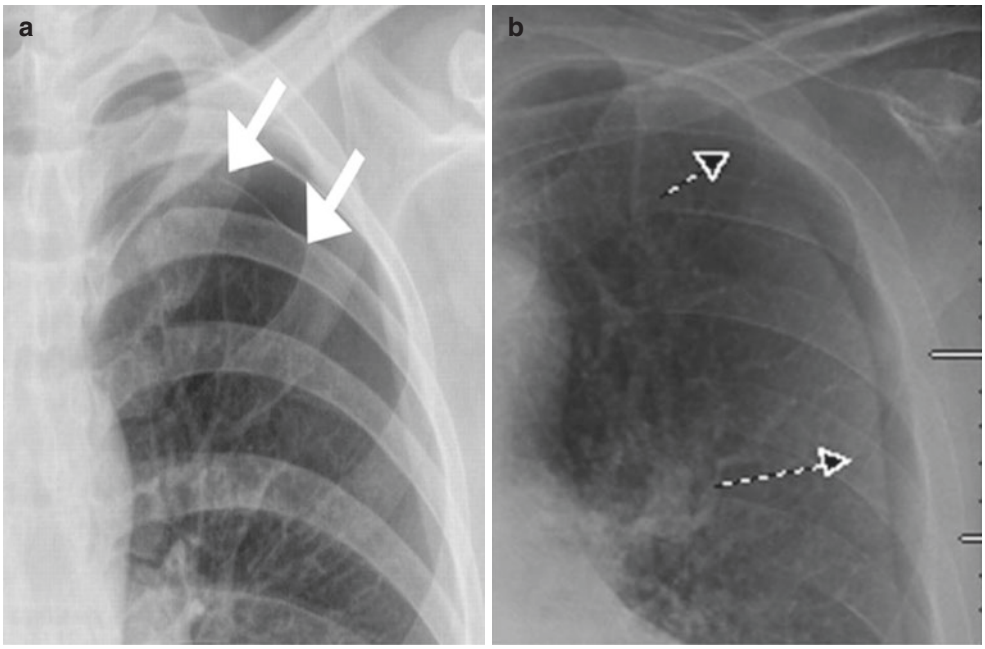

Fig. 23.2 (**a**) White visceral pleural line in pneumothorax. (**b**) Black Mach band in skin fold

Point-of-care ultrasound is increasingly used at the bedside and is the modality of choice in the ICU and ED to integrate the clinical assessment of the critically ill; in particular, lung ultrasound has advanced significantly in the last decade. Lung ultrasound can be used for early detection and management of respiratory complications under mechanical ventilation, such as pneumothorax, ventilator-associated pneumonia, atelectasis, and pleural effusions [31, 32]. Beside ultrasonography offers several advantages over chest radiography or CT scans including rapid availability, lack of radiation, real-time interpretation, and lower cost. It also offers the ability to immediately rule out a pneumothorax after an invasive procedure or in the midst of a clinical deterioration.

Clinical Scenarios in Cancer Patients

The common ED clinical scenarios involving a cancer patient presenting with a pneumothorax include the following:

1. *Secondary spontaneous pneumothorax in patients with underlying lung disease (e.g., emphysema) and a concomitant cancer diagnosis:* In fact, most cancer patients presenting with a secondary spontaneous pneumothorax had lung cancer (20%) or underlying chronic obstructive pulmonary disease (COPD or emphysema) (52%) [33]. The mechanisms could be due to bronchopleural fistula within a necrotic tumor, tumor-induced rupture of a subpleural bleb, or direct invasion of the pleura. These patients require hospitalization for observation, and potentially, chest tube insertion. Definitive surgical interventions, such as pleurodesis or wedge resection, may be required. As would be expected, patients with active cancer have a significantly worse survival compared to those without active cancer (3 vs. 113 months) [33].
2. *Iatrogenic pneumothorax following diagnostic procedures:* CT-guided or bronchoscopic lung biopsies, as well as therapeutic procedures, such as thoracentesis, bronchoscopic endobronchial tumor ablations, or percutaneous radiofrequency ablation, may produce pneumothorax. CT-guided biopsy is often considered when the abnormality is not easily accessible with a bronchoscope but the procedure is associated with higher rate of complications. For CT-guided core biopsy, the pooled rate of pneumothorax was 25.3%, pulmonary hemorrhage 18.0%, and hemoptysis 4.1%. For FNA procedures, these rates were lower, 18.8%, 6.4%, and 1.7%, respectively [34]. A high level of suspicion should exist in patients who undergo CT-guided biopsy and present with worsening dyspnea, cough, chest pressure, or pain. Usually symptoms occur within 3 h after the procedure; however, onset can be delayed in a small percentage (<4%) of patients [35]. Approximately 20% of patients with this complication require chest tube insertion, depending on the size of the pneumothorax and associated symptoms. Predisposing factors include distance of the target to the pleura, number of needle passes traversing normal lung, and presence of underlying lung diseases [36].
3. *Treatment-related pneumothorax secondary to thoracentesis, bronchoscopic ablation of central airway obstruction, percutaneous radiofrequency ablation, or chemo-induced tumor necrosis:* With the use of ultrasound, the rate of pneumothorax post-thoracentesis has dropped to less than 0.63% [35]. When a pneumothorax occurs, it is usually small and only a third of patients

require chest tube insertion. A chest tube should be considered if the pneumothorax is large or progressive and the patient is symptomatic or requires mechanical ventilation.

Central airway malignant obstruction is currently aggressively treated with several minimally invasive bronchoscopic interventions. One third of patients with advanced lung cancer develop central airway obstruction, and several other malignancies may metastasize to the airway. Pneumothorax after an ablative bronchoscopy, although rare, is usually immediate and treated in the bronchoscopy suite. It is most often related to supportive care, such as jet ventilation during rigid bronchoscopy. Nevertheless, pneumothorax must be ruled out in symptomatic patients presenting after any ablative bronchoscopy.

Image-guided percutaneous therapies became popular over the last two decades for the treatment of pulmonary malignancies, especially in nonsurgical candidate patients. They include radiofrequency or microwave ablation. Pneumothorax, pleural effusion, and subcutaneous emphysema were observed after radiofrequency ablation, respectively, in 15.9%, 20%, and 5% of patients in a recent study by Picchi et al. [37].

Pneumothorax is the most common peri-procedural complication after microwave ablation with an incidence of 33.9% and only 11% of these patients require intervention [37, 38]. Risk factors are similar to CT-guided biopsies. In addition, the number of tumor ablations during a single procedure and lack of prior lung surgery are risk factors as well. Patients with underlying emphysema are at increased risk of pneumothorax [39].

Treatment

Simple manual aspiration using an intercostal needle or small catheter is indicated in noncomplicated patients presenting with the first episode of a large or symptomatic secondary spontaneous pneumothorax. The most recent Cochrane review concluded higher immediate success rates in the needle aspiration (NA) group compared to chest tube drainage and shorter hospital length of stay in the NA group [40]. Treatment consists of inserting a needle or catheter in the pleural space, aspirating the pleural air, followed by removal of the needle or catheter. The resolution rate is high [41]. When simple aspiration is unsuccessful to keep the lung inflated or when air leak is large or persistent, a tube thoracostomy is indicated. There is no evidence that large tubes (20–24 F) are any better than small tubes (10–16 F) in the management of pneumothoraces. The initial use of large (20–24 F) intercostal tubes is not recommended, although it may become necessary to replace a small chest tube with a larger one if there is a large air leak preventing complete reinflation of the lung [42].

The most common position for chest tube insertion is in the mid-axillary line. This position minimizes the risk of injury to underlying structures, such as the viscera and internal mammary artery. For apical and large pneumothoraces extending to the apex, an antero-apical approach is favored. It requires minimal positioning and rotation of a critically ill patient. The second intercostal space in the mid-clavicular line is often chosen: two fingerbreadths from the lateral sternal border. The internal mammary vessels are at risk and bedside ultrasound may be very helpful in choosing the optimal location while avoiding vascular structures. In patients with persistent air leaks, one-way endobronchial valves are an alternative to surgical intervention [43].

Pleural Effusion

Patients with cancer frequently develop pleural effusions. Of 5888 pleural effusions collected from consecutive patients and analyzed in a single laboratory over a 14-year period, Johnston, et al. reported that 584 (9.9%) samples taken from 472 patients contained malignant cells. Leading etiologies of malignant pleural effusions (MPE) in both sexes were lung cancer (35.6%), lymphoma/leukemia (15.9%), breast cancer (14.8%), female genital cancer (8.1%), and gastrointestinal malignancies (5.9%). The incidence of cancer with unknown primary was 10.2% [44]. Fifteen to 40% of patients with MPE are asymptomatic at the time of diagnosis [45]. On chest imaging, a majority of MPE present as ipsilateral effusions, and approximately 10–13% are bilateral [46]. A quarter of all pleural effusions in a general hospital are due to cancer, and up to 50% of patients with a variety of metastatic malignancies develop a paramalignant or malignant pleural effusion. In addition, 30–70% of all exudative pleural effusions are malignant [47, 48]. Paramalignant pleural effusions are caused by tumor effects on surrounding structures; pleural fluid cytology and pleural biopsy are usually free of cancer cells. Malignant pleural effusions are caused by direct invasion of the pleura, and fluid cytology or pleural biopsies may be positive for malignant cells.

Nearly all malignant or paramalignant pleural effusions become symptomatic. It is advisable to treat these effusions upon presentation, especially if moderate to large in size, since their recurrence may hinder and delay therapy for underlying malignancy. Several important questions face the emergency physician when evaluating patients with malignant pleural effusions. Does the effusion need to be drained? What is the volume of fluid that can be drained safely at one time? What is the appropriate size of the chest tube?

Drainage

Since symptoms are frequent in patients with cancer and pleural effusion, drainage is recommended. For patients who

do not require admission after drainage, a simple therapeutic thoracentesis is recommended. We advocate the use of an 8-French pleural drainage catheter, inserted in the posterior axillary line under ultrasound guidance with gravity drainage. We prefer gravity drainage to repeated manual aspirations as it avoids steep fluctuations in negative pleural pressure, results in slower re-expansion of the lung, and allows for pleural pressure monitoring when indicated [49].

Amount of Drainage

Initial thoracentesis is a simple procedure providing symptomatic relief after acute presentation, as well as allowing assessment of the degree of lung re-expansion, which may be important to determine future management strategies. It has been advocated to drain only 1.5 liters during therapeutic thoracentesis, the rationale being to minimize the risk of re-expansion pulmonary edema (REPE) [50]. We believe in draining the majority of the pleural effusion as much as tolerated by the patient for several reasons: One, the incidence of REPE is extremely rare and typically patients develop early mild symptoms (cough and chest pressure) allowing termination of the procedure [50]. Two, in order to assess whether the patient is a candidate for future pleurodesis with a post-thoracentesis chest radiograph, one needs to document the juxtaposition of visceral and parietal pleura. Three, draining the majority of pleural effusion provides the optimal and longest symptomatic relief in between recurrences. The common side effects from large-volume thoracentesis are cough and chest discomfort, believed to be secondary to the sharp drop of intrapleural pressure [50]. Therapeutic thoracentesis should be interrupted in case of development of symptoms, as they may precede more severe complications, such as REPE, if drainage continues. Once symptoms develop, patients should limit deep breathing and refrain from talking in long sentences as further stretching the lung may lead to worsening symptoms. These symptoms typically resolve spontaneously. There is evidence that application of noninvasive positive-pressure ventilation lessens the degree of intrapleural pressure drop during large volume thoracentesis [51].

Chest Tube Size

Small-bore chest drains (defined as size < 16 Fr) are now used extensively in MPE drainage and are recommended in major guidelines (e.g., 2010 British Thoracic Society guidelines) [52]. However, the optimal chest tube size for pleurodesis has not been identified. Older case/comparative studies and one RCT suggested that small bore drains are effective for pleurodesis; unexpectedly, a higher complication rate has also been reported. If presenting with recurrent large malignant pleural effusion, we recommend small-bore (8–16 Fr) chest tube insertion in the posterior axillary line, with connection to a Pleur-evac® system (Teleflex, Morrisville, NC) without wall suction or gravity drainage bag. We also advocate early pulmonary consultation in order to plan for long-term fluid management strategies. We do not see any advantages to large-bore chest tube insertion, as documented in previous studies [53].

Indwelling pleural catheters (IPCs) should be considered first-line management of MPEs, in conjunction with standard talc pleurodesis. Recognition of the advantages and disadvantages of each approach allows patients to choose an option. It is acknowledged that the use of IPCs without pleurodesis agents can lead to spontaneous pleurodesis [42, 54], allowing removal of the catheter. In patients who desire faster removal of the catheter, a more aggressive drainage regime or instillation of talc via the IPC is a judicious option [55]. Some special situations may face emergency physicians with patients carrying tunneled pleural catheters who present for worsening symptoms due to inability to drain fluid or clogged catheters. Pulmonary consultation is suggested in these situations, as an evaluation of the pleural space with chest radiograph or thoracic ultrasound is required to evaluate for residual pleural fluid. In cases of clogged tunneled pleural catheters with significant residual pleural fluid, intrapleural catheter instillation of alteplase may be indicated to unclog the tube [55].

Summary

Pleural effusion and pneumothorax are common pulmonary manifestations in patients with cancer, most commonly occurring after required interventions treating the primary malignancy. Early recognition and intervention are indicated as delays may interfere with cancer treatment. Small-bore chest tubes are as good as large bores tubes and should be used primarily. Talc pleurodesis and indwelling pleural catheters effectively manage the symptoms of MPE. The use of bedside ultrasound has improved diagnostic accuracy and minimized complications.

Hemoptysis

Etiologies

One of the most common causes of hemoptysis is lung cancer, along with inflammatory and infectious etiologies, such as bronchiectasis, bronchitis, and tuberculosis [56]. During their lifespan, 20% of patients with lung cancer develop hemoptysis. Non-small-cell lung cancer patients have a higher incidence than small cell. Other malignant causes include endobronchial metastatic carcinoma (melanoma, breast, colon, or renal cancer), bronchial carcinoid in young patients, and Kaposi sarcomas in AIDS patients. Hemoptysis can also be chemotherapy induced, caused by necrosis of large tumors or potential medication side effects. With the

development of several antiangiogenic agents inhibiting vascular endothelial growth factor for the treatment of advanced lung cancer, more patients are started on those agents as they progress with their disease. One of the reported side effects of these agents, for example, bevacizumab, is hemoptysis. When hemoptysis from bevacizumab occurs, it is often massive. In fact, life-threatening hemoptysis has been reported in up to 9% in patients receiving bevacizumab [57] and most of the hemorrhages were fatal, occurring during the initial cycles of treatment [58]. It is therefore important to recognize and attribute hemoptysis in patients receiving bevacizumab and realize that it is often fatal. Early critical care and interventional pulmonary or radiology consults are crucial in patients receiving bevacizumab presenting with hemoptysis, even if mild.

Massive Hemoptysis

The definition of massive hemoptysis remains poorly defined in the literature because terms used to describe the amount of hemoptysis are inconsistently utilized. Life-threatening or massive hemoptysis is characterized by a larger volume of blood, while clinical instability is considered to be a better indication of poorer outcome. Reported thresholds for massive hemoptysis in the literature range from 100 to 1000 mL in a 24-h period [59]. In our opinion, massive hemoptysis is present when a patient is coughing more than 100 ml/24 h and raises concerns as to airway protection issues or gas exchange impairment. Massive hemoptysis is the cause of death in 3% of patients with lung cancer. Urgent diagnostic and therapeutic interventions are advised in patients with massive hemoptysis. Several initial steps are important upon presentation: localize the source, protect the airway, optimize gas exchange, and then control the bleeding. A multidisciplinary team approach (pulmonology, interventional pulmonology, interventional radiology, and surgery) should be undertaken as soon as the condition is identified [60].

Clinical suspicion, previous history, and available previous imaging are important in localizing or estimating the location of the bleeding. The suspected bleeding site should be placed in a dependent position in order to prevent spillage or formation of large blood clots into the nonbleeding lung. If massive bleeding is associated with significant symptoms, endotracheal intubation should be performed using at least an 8.0 mm endotracheal tube (ETT). A large ETT tube facilitates access for the therapeutic bronchoscope and provides a route for laser coagulation or cryoprobe-assisted removal of large blood clots. Additionally, the tip of the ETT can be pushed deep into the nonbleeding main bronchus to further protect the nonbleeding side from blood contamination. This maneuver obviously requires bronchoscopic guidance. After intubation, mechanical ventilation may be initiated with optimized settings to achieve adequate oxygenation and ventilation. Also, correction of any underlying coagulopathy is warranted.

Bronchoscopy with instillation of epinephrine or ice-cold saline is a temporary measure to potentially control bleeding until laser ablation equipment is available for more permanent control. Use of iced saline has become common practice. Endobronchial epinephrine and norepinephrine are also commonly used; however, recommendations for safe dosage and concentration vary quite widely in the literature. In contrast to iced saline, the safety of endobronchial epinephrine has been questioned, given reports of coronary vasospasm and arrhythmia [61].

Bronchoscopic measures are effective only for bleeding sites within the reach of the bronchoscope. Otherwise, arteriographic localization of a bleeding site and embolization is the method of choice to control bleeding from peripheral sites not easily reached through the airway [62]. Surgical evaluation and possible intervention are indicated in case of an uncontrollable bleeding site [63]. Surgical intervention in bleeding patients is associated with significant morbidity and mortality [64]. Tranexamic acid (TXA), an antifibrinolytic medication that competitively inhibits plasminogen activation, has been prospectively studied in groups of submassive hemoptysis in both IV and nebulized form. TXA was associated with a decrease in hemoptysis and need for interventional procedures [65]. Additionally, recombinant activated factor VII and recombinant thrombin have also been used in cases of hemoptysis due to diffuse alveolar hemorrhage with moderate hemoptysis [66–68]. One-way endobronchial valves have also been used in a small study of patients with moderate hemoptysis [69]. Most available literature on massive hemoptysis is limited.

Summary

Hemoptysis in cancer patients is a serious manifestation of airway involvement or chemotherapy side effect. Hemoptysis is often massive and potentially fatal in patients receiving bevacizumab. Early intervention and consultation of specialized services are crucial steps in the management of massive hemoptysis.

Chemotherapy and Radiation-Related Pulmonary Toxicities

Chemotherapy-Related Pulmonary Toxicity

Acute Complications

Immune Checkpoint Inhibitor-Related Pulmonary Toxicity Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment and are now a standard of

care for a variety of cancers in both metastatic and adjuvant settings. Despite the clinical benefits of the ICI therapy, they are not without complications and can affect multiple organs. ICI-associated pneumonitis is an uncommon, but potentially serious, adverse event.

Lung Toxicity ICI-associated pneumonitis is defined as focal or diffuse immune-related inflammation of lung parenchymal cells and ICI-induced pneumonia is defined as the infection of lungs after ICI treatment. The incidence of pneumonitis is variable in clinical trials, ranging between 3% and 5% [70]. The overall mortality rate associated with all PD-1/PD-L1 inhibitors is about 0.45% but ICI-induced pneumonitis is the most common reason for death among patients treated with ICIs [71].

The duration from ICI administration to onset of pneumonitis is variable (2–24 months). Early onset of ICI pneumonitis was found to be more severe in one study [72]. No definite clinical symptoms, characteristic CT manifestations, or serological markers are available to establish a diagnosis of ICI-induced pneumonitis. It is usually a diagnosis of exclusion after an extensive evaluation for potential infectious etiologies. Computed tomography (CT) usually displays reticular infiltrates with ground-glass opacities and consolidation in patients receiving PD-1 inhibitors [73]. Supportive care and empiric antibiotics are recommended during the initial treatment. Most ICI-associated pneumonitis cases are corticosteroid therapy responsive; however, 15–30% of cases can show a poor response to therapy, leading to a poor prognosis for these patients. High-dose steroids are advised with a taper over 6 weeks or longer.

Conclusion

Treatment with immune checkpoint inhibitors induces a variety of adverse events, which can sometimes be serious or fatal, albeit infrequent. Among them, pneumonitis is one of the most life-threatening adverse events. Currently, no optimal management guideline exists for the management of pneumonitis, but it usually responds to immunosuppressive medications.

Conventional Chemotherapy-Related Pulmonary Toxicity

Pulmonary toxicity from antineoplastic agents is common. The exact incidence of lung toxicity remains unclear; this is related to confounding factors, including pulmonary comorbidities and prior or concurrent use of other treatment modalities, such as radiation and antineoplastic drugs. It is estimated that approximately 10–20% of patients receiving chemotherapy develop some form of lung toxicity [74, 75]. Pulmonary injury can vary from mild to severe and is divided into acute and delayed onset [76]. The acute onset syndromes include inflammatory interstitial pneumonitis, pulmonary edema, bronchospasm, and pleurisy or pleural effusion, typically presenting after the first one or two cycles of the administered agent.

The inflammatory interstitial pneumonitis syndrome is a hypersensitivity-like reaction. It is the most common chemotherapy-associated lung injury [76]. It has an acute to subacute presentation with productive cough and worsening dyspnea, associated with low-grade fevers and fine crackles on physical exam. A chest radiograph shows either an interstitial or mixed interstitial and alveolar pattern. The most common agents associated with this syndrome are methotrexate, bleomycin, procarbazine, and carmustine. It can mimic an atypical pneumonia or hypersensitivity pneumonitis. The prognosis is generally favorable with simple discontinuation of the offending agent and treatment with corticosteroids for more severe cases.

The pulmonary edema syndrome, less common than interstitial pneumonitis syndrome, has a more acute presentation. Caused by endothelial inflammation and vascular leak, it leads to noncardiogenic pulmonary edema (NCPE). Patients may present with severe dyspnea. Cough, fatigue, and increased work of breathing may also be present, sometimes associated with profound hypoxemia and crackles on physical exam [77]. Chest radiograph shows similar findings to those found in patients with pulmonary edema but with a normal size heart. It is typically a diagnosis of exclusion after establishing normal cardiac function in a clinical picture of congestive heart failure. Chemotherapeutic agents most commonly associated with NCPE are (by order of frequency) cytarabine, interleukin 2, trans-retinoic acids, and gemcitabine. A higher incidence of NCPE has been reported in patients undergoing allogenic and autologous bone marrow transplant, beginning with induction chemotherapy [78, 79].

Bronchospasm and asthmatic-like reactions can also occur with chemotherapy agents. They have been reported upon exposure to the first cycle. Two mechanisms are responsible: IgE and non-IgE related. The chemotherapy agents causing IgE-related bronchospasm are platinum compounds, such as cisplatin, carboplatin, and oxaliplatin. Those causing non-IgE-related bronchospasm are taxanes (paclitaxel and docetaxel), asparaginase, and epipodophyllotoxins (etoposide and teniposide). In the acute setting, anaphylactoid reactions in the absence of hypotension should be treated with intramuscular injections of epinephrine 1:1000, 0.5 mg per single dose. In the presence of severe hypotension or shock, continuous intravenous infusion of epinephrine is recommended. Antihistamines and corticosteroids, as well as bronchodilators and supplemental oxygen, are also indicated.

Pleurisy or pleural effusion can be a manifestation of chemotherapy-induced side effects with methotrexate. When administered in high doses, it may cause chest pain, sometimes 2–5 days later, in 2–4% of patients. Thirty percent of those may progress and develop pleural effusion [80]. Pain typically subsides 3–5 days after discontinuation of the drug and may relapse if the offending agent is restarted [81].

Late Complications

Late-onset chemotherapy-related pulmonary complications usually present 2 months after completion of therapy. The most common manifestation is pulmonary fibrosis. The agents most commonly associated with this complication are bleomycin, busulfan, carmustine, and mitomycin-C. Common risk factors for this toxicity are advanced age, concomitant radiation treatment, or combination chemotherapy. The use of supplemental oxygen, even at low flow rates, amplifies bleomycin toxicity and may play a role in the development of pulmonary fibrosis, even years after treatment [82].

Patients typically present with the insidious onset of dyspnea associated with nonproductive cough. Physical examination reveals crackles and chest radiograph shows bibasilar reticular interstitial markings. Pulmonary function tests may be consistent with restrictive disease. History and physical examination with elimination of other underlying issues, such as congestive heart failure, are essential to the diagnosis. Bronchoscopy may be useful in ruling out lymphangitic spread as well as infectious etiologies. Definitive diagnosis may require video-assisted thoracoscopic surgery. Supportive treatments and a trial of corticosteroids are mainstays of therapy; however, use of oxygen in patients who have bleomycin lung toxicity should only be used in those with severe hypoxemia.

Radiation-Related Pulmonary Toxicity Radiation-induced lung injury (RILI) encompasses any lung toxicity induced by radiation therapy (RT) and manifests acutely as radiation pneumonitis and chronically as radiation pulmonary fibrosis [83]. Radiation-induced lung injury results from the combination of direct radiation cytotoxicity in addition to radiation-induced cellular signal transduction. This cellular activation initiates a repair process that involves cytokines and growth factors, such as basic fibroblast growth factor, interleukin-1, and transforming growth factor-beta, leading to the development of fibrosis. The incidence of serious pulmonary complications from radiation therapy has decreased secondary to advances in radiation delivery techniques. More recent data suggest RILI incidence is highest for lung cancer (5–25%), followed by mediastinal lymphoma (5–10%) and breast cancer (1–5%) [84].

Several risk factors have been described, including volume of lung irradiated, total dose of radiation >60 Gy, number of fractions delivered, concomitant chemotherapy, previous radiation treatment, and weaning of systemic steroids. Age is not a risk factor but radiation pneumonitis seems to be worse in elderly patients. Radiation pneumonitis occurs within 6 months of therapy (most often within 12 weeks), whereas radiation pulmonary fibrosis occurs >1 year following therapy [85]. If symptoms begin earlier, patients tend to suffer a more severe course. The severity of radiation pneumonitis varies from radiographic findings with no clinical symptoms to life-threatening disease requiring hospitalization [86]. The most common symptom is dyspnea, which may be associated with a pinkish productive cough. The diagnosis is usually clinical and based on the timing of radiation treatment and typical chest radiograph findings corresponding to the field of radiation. Clinically significant radiation-induced pulmonary fibrosis typically occurs months to years following therapy and is described as progressive dyspnea associated with lung scarring. Tachypnea and cyanosis are both signs of advanced disease.

Bronchoscopy is rarely helpful and serves only to rule out an infectious or recurrent malignant process. Corticosteroid therapy is commonly used, although its efficacy is controversial. Prednisone (1 mg/kg or equivalent doses of other corticosteroids) is indicated for acute radiation pneumonitis, but not in fibrosis. Therapy should be continued for 2–4 weeks, followed by a slow tapering of the medication for an additional 6–12 weeks [87]. The only two drugs that have shown efficacy in reducing rates of pneumonitis in humans are amifostine and pentoxifylline in combination with tocopherol. Amifostine is the only FDA-approved drug, but its use is limited because of adverse effects [88].

Another reported and more acute form of radiation-induced lung injury is radiation-related bronchiolitis obliterans with organizing pneumonia (BOOP) [89]. Most reported cases occur among patients irradiated for breast cancer. Common manifestations include cough and fever and, to a lesser degree, dyspnea. The radiographic findings begin in the radiation field but may progress even to the contralateral lung in 40% of cases. Patients respond dramatically to corticosteroids but also carry the risk of significant relapse if tapered in a short period of time.

Summary

Radiation pneumonitis often progresses to lung fibrosis and is typically limited to the radiation field. Clinical and radiographic suspicions are important in establishing the diagnosis. Radiation-induced BOOP is a more acute form that often involves the contralateral lung. Treatment with corticosteroids should be tapered slowly in order to avoid the risk of a relapse.

Nonthrombotic Pulmonary Embolism (NTPE)

NTPE is the embolization of nonthrombotic tumor material into the pulmonary circulation, blocking it either entirely or partially. The nonthrombotic tumor material in patients with cancer includes macro- or microembolism. It is called pulmonary tumor embolism (PTE). These emboli are distinct from true metastases as they remain intravascular and rarely invade the pulmonary parenchyma. With complete occlusion, necrosis of the dependent pulmonary parenchyma similar to a thrombotic event follows. When partially occluding the vascular lumen, inflammatory reaction, vascular intimal proliferation, and activation of the coagulation cascade may develop. The reported incidence of this complication is difficult to assess and is reported at 2.4–26% based on postmortem examination [90, 91]. This variability reflects the difficulty in diagnosing this syndrome. There is predominance of digestive system and liver tumors associated with PTE; breast cancer and cardiac lymphomas have also been reported, but at a lesser rate. The risk of tumor embolization is increased among patients undergoing chemotherapy, radiation, or surgical intervention (fragmentation and embolization of tumor fragments or cells). The presentation is often insidious, progressing over several weeks to months. In rare instances, it can be acute (10–20%) [92]. In patients with proximal and large tumor emboli, the presentation can be dramatic and acute with signs of right heart failure. Patients typically present with worsening dyspnea, cough, and increased work of breathing, sometimes associated with ascites and peripheral edema, reflecting increased right heart pressure. The gold standard test is pulmonary artery blood cytology, obtained through a pulmonary artery catheter. Though PTE is not considered to be metastasis, the prognosis is still poor. Treatment is supportive and should be directed to the primary tumor. Chemotherapy does not generally affect the prognosis of patients with PTE unless the primary tumor is very chemotherapy responsive (e.g., trophoblastic or Wilms tumors).

Summary

PTE syndrome is often the result of tumor destruction, whether with medications or surgical intervention. Symptoms are insidious, however, may mimic thrombotic events. Diagnosis is often clinical but occasionally can be made with pulmonary artery blood cytology. Prognosis is generally poor.

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Venous Thromboembolism

24

Nicholas R. Pettit and Jeffrey A. Kline

Case Study

A 55-year-old male presents to the emergency department (ED) with chest pain. It started about 1 day ago, constant in nature, substernal, nonexertional, and pleuritic. He took some acetaminophen without any relief. He has had some dyspnea on exertion for the past week, but no fever, chills, myalgias, leg pain, or swelling. He has had some anorexia because he is undergoing chemotherapy, and last received gemcitabine 2 weeks ago. His vital signs are blood pressure of 145/85, heart rate of 75 beats per minute, SpO_2 99% on room air, and a temperature of 37.4 °C. He is comfortable in the bed and otherwise is well appearing in no acute distress. You suspect pulmonary embolism, order troponin and pro-BNP which return normal, and the ECG is sinus rhythm unchanged from his previous. Remainder of labs including BMP and CBC are within normal limits. CT scan of his chest demonstrates several small subsegmental pulmonary emboli without any evidence of right heard strain. As the treating practitioner in the ED, you are responsible for this patient's disposition, and ultimately decide to discharge this patient after communication with the patient's oncologist. Application of the Hestia criteria determines that the patient is low risk for outpatient management of his pulmonary emboli, so you prescribe rivaroxaban and discharge the patient home after arranging follow-up with his oncologist in 2 days.

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Pathophysiology of Thromboembolism in Cancer

Annually, 1.5 million patients will receive a new diagnosis of cancer in the United States, of whom 5% or 75,000 patients will receive an additional diagnosis of venous thromboembolic disease (VTE). VTE is a direct complication of cancer and is known to be influenced by tumor type, stage, and active treatment [1]. The risk of VTE is 53-fold higher than baseline in the first 3 months after diagnosis of cancer and remains approximately fourfold higher until 15 years after initial cancer diagnosis [2]. Carrying a dual diagnosis of both cancer and pulmonary embolism (PE) is associated with worsened prognosis, increased recurrence rates, longer duration of anticoagulation, and worsened bleeding risks.

In healthy patients, the vessel endothelium prevents thrombus formation by acting as a barrier to the underlying subendothelium, which contains tissue factor (TF). When TF is exposed through vessel wall damage, it complexes with circulating Factor VIIa and initiates the extrinsic pathway, the primary driver behind the entire coagulation cascade. To initiate a clot, TF must bind with circulating Factor VIIa. This results in a complex capable of converting Factor X to Xa, which cleaves prothrombin to thrombin, in turn cleaving fibrinogen to fibrin, leading to a cross-linked fibrin clot after the action of Factor 13, itself activated by thrombin. Cancer increases the exposure of TF to the blood by several mechanisms, including the surface characteristics of cancer cells, their production of TF-bearing microparticles, and by direct vascular damage as a result of tumor spread. As an example, pancreatic cancer, a highly thrombogenic malignancy, causes significant elevations in microparticle-associated TF, leading to rates of VTE as high as 45% in some series [3, 4]. In addition to increased production of TF, cancers can also release various proinflammatory cytokines, interleukins, and procoagulants [5].

Cancer patients undergo a variety of procedures and treatments that further increase their risk for thrombosis. Surgery, chemotherapy, and radiation therapy cause a proinflammatory

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state, and some chemotherapeutic agents produce a prothrombotic state that independently increases clotting risk, notably fluoropyrimidines, L-asparaginase, and thalidomide derivatives [6, 7]. The chemotherapeutic agents Ara C and 5-fluorocytosine alter the metabolism of coumarins and complicate the ability to achieve stable anticoagulation. In addition, interrupting anticoagulation for procedures in patients with active VTE has been associated with increasing rates of postoperative thrombotic and bleeding complications [8]. Cancer patients frequently have other risk factors for VTE including indwelling catheters, immobility, and folate deficiency [9].

Thrombogenic Cancers

Emergency physicians will often consider the need to test for VTE while treating patients with cancer. However, thrombogenicity varies with host factors, tumor stage, and type. In general, the more undifferentiated the cell type and the larger the tumor burden, the higher the risk. The incidence of VTE in a large study population demonstrated a rate of 2% of all cancer patients, with increased rates seen among patients with metastatic disease, pancreatic cancer, and colon cancer [10]. Cancers that appear to confer no or minimal risk of VTE include localized breast, cervical, prostate, and nonmelanomatous skin cancers, such as squamous cell carcinoma and basal cell carcinoma. However, advanced stage breast cancer or breast cancer patients undergoing chemotherapy may have a thrombosis risk of up to 10% during treatment [11, 12]. Similarly, treatment of leukemias, particularly acute lymphocytic leukemia treated with L-asparaginase and acute promyelocytic leukemias treated with all-trans-retinoic acid have each been associated with an approximate 10% incidence of VTE throughout the course of therapy. Other cancers that are particularly thrombogenic include adenocarcinoma, glioblastoma, melanoma (in contrast to other skin cancers), lymphoma, and multiple myeloma [13]. Pancreatic, gastric, ovarian, and renal cell cancers carry notoriously high risks. Finally, in addition to different risks based on malignancy types, within the California Cancer Registry (CCR), racial disparities exist with non-Hispanic whites and African Americans having an incidence of VTE almost twice that of Hispanic and Asian patients. This may be due in part to variable expression patterns in different ethnic groups, but the basis for these disparities are mostly undefined [14, 15].

Clinicians should be especially vigilant for VTE during the induction phase of chemotherapy, as this is the most thrombogenic period [16]. L-asparaginase and bolus fluorouracil treatment confer particularly high thrombosis risks, probably by reducing antithrombin concentrations [17]. While localized breast cancer has a relatively low thrombogenic potential, risk approximately doubles with tamoxifen treatment, whereas aromatase inhibitors do not appear to increase risk. Concomitant treatment with red cell growth factors such as erythropoietin clearly increases risk of thrombosis, regardless of tumor type or stage [18]. Any patient who presents with extremity swelling or chest pain during the initial treatment phase with these drugs should undergo diagnostic studies outlined in Table 24.1 to exclude thromboembolism. Similarly, multiple myeloma patients treated with lenalidomide or thalidomide are at risk, although one large Japanese cohort study found this to be 1.4% and at baseline for their cancer [19, 20]. Bevacizumab presents a complex picture, with some studies suggesting a high risk and a more recent systematic review showing no increase compared with matched patients receiving other forms of chemotherapy for similar tumors [21]. A clinical prediction rule has been developed [18] to determine which cancer patients are at highest risk for future thrombosis. In this model, patients with ≥3 points are found to have VTE risks of approximately 7%. Lastly, a recent systematic review and meta-analysis reports a pooled VTE rate of approximately 7% among cancer patients receiving neoadjuvant therapy, with highest rates among those with bladder and esophageal cancers [22].

Table 24.1 Diagnostic criteria required to exclude venous thromboembolism in cancer patients

Deep vein thrombosis	Pulmonary embolism
Negative full leg duplex ultrasonography[a]	Adequate quality negative CTPA
Negative (<500 ng/μL) d-dimer plus negative proximal ultrasound	Negative homogenous perfusion scan
Two negative proximal ultrasounds 2–7 days apart[b]	Low probability V/Q scan and a single negative bilateral whole-leg lower extremity duplex ultrasonography or two negative proximal ultrasounds 2–7 days apart

CTPA Computed tomography pulmonary angiography, *V/Q* A ventilation–perfusion scan

[a]Full leg ultrasound includes spectral and B-mode compression imaging of the proximal and distal femoral vein, the popliteal, posterior tibial, peroneal and greater saphenous veins

[b]Proximal ultrasound includes spectral and B-mode compression imaging of the proximal and distal femoral vein and the popliteal vein

What Does VTE Mean for the Cancer Patient?

Cancer patients who develop VTE have higher morbidity and mortality risks. This risk represents the synergistic effect between the two disease entities. Diagnosis of VTE in cancer confers several independent, negative consequences, including a reduced overall probability of survival, indication of more aggressive cancer, and a higher risk of bleeding from anticoagulation than noncancer patients that suffer from VTE [23]. In addition, cancer-associated nausea impairs oral anticoagulant administration and absorption. Pill fatigue can impair anticoagulation therapy compliance, as these patients

are often on multiple medications. For those receiving vitamin K antagonists (VKAs) such as warfarin, the additional needle sticks for INR checks can be onerous. Finally, cancer patients tend to experience higher severity of clot burden than patients without cancer. In the authors' experience, these thrombi are larger and more extensive in both the extremities and in the lung, leading to a larger disease burden and increased incidence of postthrombotic syndrome.

Special Considerations for Diagnosis

The diagnostic approach to a cancer patient with suspected VTE mirrors that of other moderate- to high-risk patients with suspected PE (see Table 24.1). Unfortunately, while being at higher risk for thrombosis, cancer patients are also at higher risk for complications from diagnosis. One such currently debated topic is that of contrast-induced nephropathy (CIN), as older literature illustrates an increased risk of CIN in all outpatients receiving contrast-enhanced computed tomography, as well as in active cancer patients receiving contrast-enhanced CTs [24, 25]. More recently, however, in a retrospective cohort comparing contrasted to noncontrasted CT scans in a cancer cohort, the rate of acute kidney injury (AKI) was independent of the administration of contrast, but instead was more associated with preexisting congestive heart failure and prior AKIs [26].

The D-dimer, which normally can be used to reliably exclude VTE because of its high sensitivity, becomes markedly less specific in the cancer population. Many cancer patients will have positive D-dimer results in the absence of clot, meaning that the test is less useful in patients with active cancer. Active malignancy induces a system-wide activation of the clotting network, and elevated D-dimer levels may herald a poor cancer prognosis without indicating thrombosis [27]. This phenomenon likely reflects important interactions between hemostatic mechanisms and tumor-associated angiogenesis and inflammatory mediators. D-dimer levels confer additional prognostic value to tumor stage and predict decreased survival for breast cancer patients, and is a marker of decreased survival in colorectal, cervical, pancreas, prostate, brain, and melanoma cancers [1]. While a negative D-dimer still helps rule out VTE, it does so in a smaller proportion of patients with active cancer.

Risk Stratification and Management

In the era of target-specific anticoagulants (TSAs, formerly referred to as direct oral anticoagulants or DOACs) such as rivaroxaban, apixaban, and dabigatran, the need to hospitalize all patients with thromboembolic event, including PE, is being called into question. It has been long held that many patients with DVT can be safely discharged home [28]. However, several caveats to this practice exist, chief among them is a low-risk status. In practice, low-risk status among those with cancer refers to the lack of a reason why the patient would need hospital care in the next 30 days. The primary determinant of success of outpatient treatment will be access to anticoagulant and ability to administer it. While the preferred method of treatment for both DVT and PE in active cancer remained injected low-molecular-weight heparin (LMWH), rivaroxaban is now an acceptable primary therapy for VTE according to The National Comprehensive Cancer Network Guidelines [29, 30]. Thus, the first objective with home treatment is to determine if the patient and caretakers have the capacity and competence to administer twice daily subcutaneous injections. Other predictors of return to the hospital are inadequate pain control, decompensation of other disease processes, need for oxygen, or hemodynamic and respiratory effects of concomitant PE, which occur in over 1/3 of patients [31]. Patients with significant iliofemoral clot burden may require admission for catheter-based therapy in view of evidence that this approach significantly decreases postthrombotic syndrome and leg ulceration, which are the major complications of these proximal, occlusive DVTs [32].

Patients with PE are increasingly treated at home, starting the same day of diagnosis, provided that these patients meet low-risk criteria [32–34]. Several criteria have been validated, including the Hestia criteria, the PESI, and sPESI scores [35–38]. However, the sPESI score excludes discharge of patients with cancer. The Hestia criteria do not exclude patients with cancer, but we suggest that cancer patients with VTE must also meet a separate set of rules, of which two have currently been published: POMPE-C and criteria derived from the Registro Informazitado Enfermo TromboEmbolica (RIETE) database by den Exter et al. [39]. These criteria include additional predictors such as metastases, immobilization, and low body weight while they also stratify cancer patients based on perceived risk of thrombosis [39, 40].

Thus, to deem a patient with either DVT or PE and with active cancer (defined as under the current care of an oncologist or receiving palliative therapy, or any patient with metastasis) as low risk for home treatment, we recommend a two-step approach. First, apply the Hestia criteria (Table 24.2) and second, for patients with confirmed PE or patients with DVT and strongly suspected PE, apply either the POMPE-C criteria (Table 24.3) or the den Exter criteria [35, 41–43]. The POMPE-C criteria predicts mortality for cancer patients with PE; however, for safe outpatient management, the Hestia criteria account for several other variables that may particularly impact cancer patients (e.g., renal dysfunction, liver disease, medical/social reasons for admission). The EPIPHANY index has been derived and validated for pre-

Table 24.2 The Hestia criteria

Patient fails criteria if any of the below are true
Hemodynamically unstable
Requires thrombolysis or embolectomy
Active bleeding or high risk for bleeding
More than 24 h supplemental O_2 required to maintain O_2 saturation >90%
PE diagnosed while currently under active anticoagulant therapy
Severe pain requiring >24 h intravenous analgesic therapy
Medical or social reason for hospitalization >24 h (infection, malignancy, no support system, etc.)
Creatinine clearance <30 mL/min
Severe liver impairment
Pregnancy
Documented history of heparin-induced thrombocytopenia

Table 24.3 The POMPE-C criteria (used in an online calculator for overall risk of death at 30 days)

If all criteria shown are absent, the patient's risk of death is sufficiently low to justify home treatment for the patient with active cancer
Absence of a *Do Not Resuscitate* order
No respiratory distress (defined by the patient showing fear, anxiety, or dyspnea)
No unilateral leg swelling
No altered mental status
Heart rate <100 beats/min
Respiratory rate <28 breaths/min
Pulse oximetry >94% on room air
Weight >140 pounds

dicting risk of serious complications from incidental PEs in cancer patients but has not been used to demonstrate safe ED-discharge among acute DVT/PE in cancer patients [44].

Treatment

At present, the recommended treatment for VTE in cancer is daily injections of 200 IU/kg bodyweight of dalteparin, a LMWH, as opposed to warfarin. The CLOT trial in 2003 demonstrated that dalteparin was superior to warfarin with a 52% risk reduction profile for recurrence of clot [45]. It is important to recognize that there is a widespread assumption that enoxaparin 1 mg/kg bodyweight (Lovenox®) is equivalent to dalteparin (Fragmin®), although this has never been demonstrated in a clinical trial.

Despite the knowledge of a risk reduction from dalteparin, patients often request oral therapy, as injections are expensive, onerous, and painful, as well as causing bruises and disfigurement [37]. While limited data suggest that patients prefer efficacy and safety over convenience [46], it is the authors' opinion that physicians underestimate the negative perceptions that patients have toward injections. Given the difficulty of self-injection and cost of the injectable LMWHs, many EDs utilize case managers or social workers to assist with the transition to outpatient therapy.

FDA-approved drugs, specifically target-specific anticoagulants (TSA), include apixaban (Eliquis®), betrixaban (Bevyxxa®), dabigatran (Pradaxa®), edoxaban (Savaysa®), and rivaroxaban (Xarelto®). These drugs offer alternative to therapies more inconvenient injectable LMWHs and VKAs as they are easier to take and less invasive for patients [47]. Furthermore, they don't require weight-based dosing, facilitating outpatient compliance and management.

Available data support a shift toward the use of orally available TSAs for treatment of patients with active cancer and VTE. The basis for this statement comes from a pooled subgroup analysis of patients with cancer at the time of enrollment in the EINSTEIN DVT and PE studies [38]. Together, these studies randomized 597 patients with either active cancer at baseline (n = 430) or cancer diagnosed during the study (n = 167) and found statistically insignificant reductions in risk of both VTE and bleeding for rivaroxaban versus standard therapy (LMWH + VKA) while producing a net clinical benefit for the composite outcome of recurrent VTE and major bleeding (hazard ratio, 0.60; 95% CI, 0.36–0.99) favoring rivaroxaban. This is reinforced by a Cochrane review suggesting that LMWHs compared to VKAs produce a reduction in VTE and in comparing TSAs to LMWHs finding a reduction in VTE but an increased risk of major bleeding [48]. Results from a trial dedicated to treating patients with VTE and active cancer suggest equal efficacy of rivaroxaban to LMWH but with a slightly higher rate of clinically relevant bleeding [49]. Lastly, comparing oral rivaroxaban to LMWH and VKA in the treatment of symptomatic VTE in cancer patients, rivaroxaban had similar efficacy and reduced number of major bleeding events as compared to LMWH/VKA but had no difference in clinically relevant bleeding [50]. It is reasonable to assume equipoise between injectable LMWH and the direct-acting anticoagulants. Figure 24.1 highlights a summary of randomized trials on TSAs in patients with cancer, both in terms of completed work and ongoing trials [51].

Deciding on which therapy to initiate in the ED should include patient preferences that might influence adherence (some patients hate injections; others with nausea may want to avoid swallowing pills) [48]. The Anti-Clot Treatment Scale is a 15-item patient report scale developed and validated for use in measuring patient-reported satisfaction with anticoagulation treatment [52]. This scale has been utilized in several trials to demonstrate that treatment with oral TSAs results in improved treatment satisfaction as compared to enoxaparin/VKA, as well as improved psychological impacts as compared to VKAs [53, 54]. Similarly, in a systemic review of patient-reported outcomes associated with TSAs, patients prefer TSAs to VKA with higher quality of life scores and increased adherence

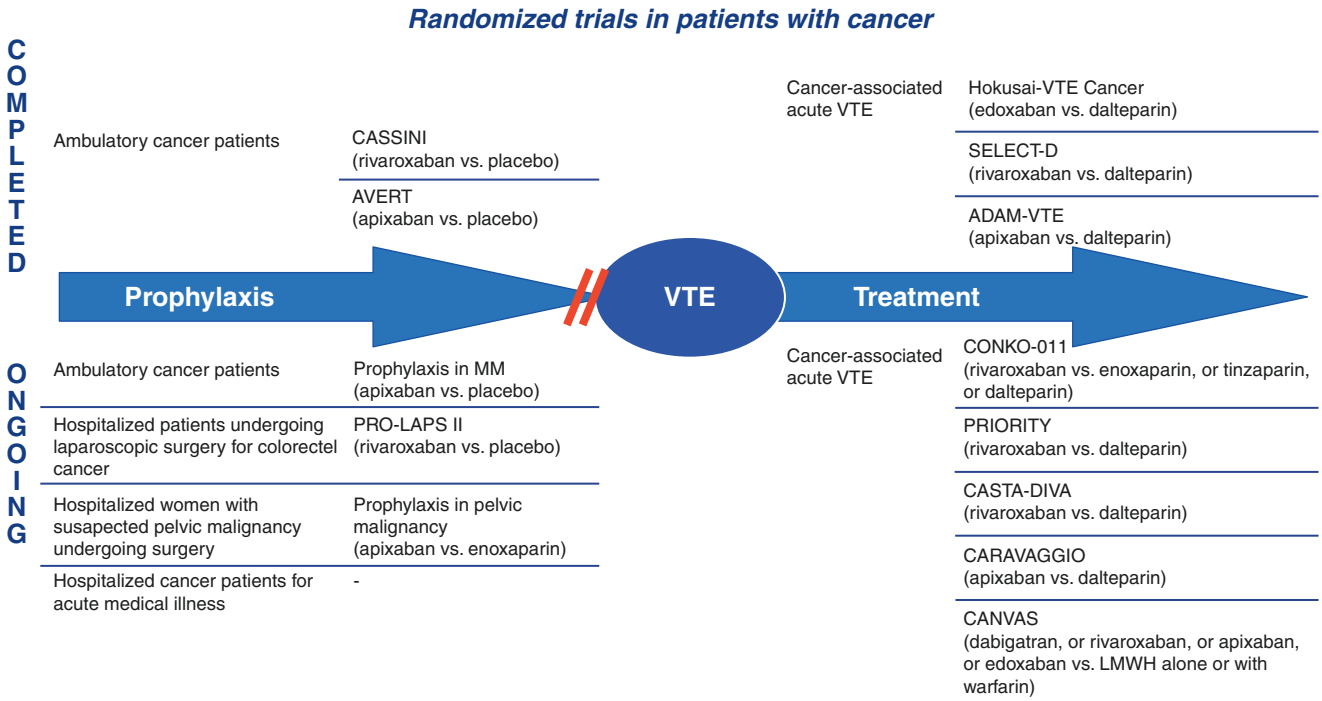

Fig. 24.1 Summary of randomized trials on target-specific anticoagulants in patients with cancer. (From Vedovati et al. [51], with permission from Elsevier)

[55]. Lastly, twice daily dosing with LMWH in cancer patients was nonsignificantly associated with a trend toward worsening perceptions of the 6-month VTE LMHW treatment, further suggesting that daily dosing is preferred, or additionally suggesting that TSAs may be more tolerable in the long term [56].

Duration of need for anticoagulation sometimes emerges as a concern in the ED, particularly for patients who present with bleeding. Although several stopping criteria have been derived [57], none are adequately validated to provide clear, binary decision-making for cancer patients. A general rule of thumb is to anticoagulate for the duration of cancer treatment and then for several months thereafter. At a minimum, cancer patients with any venous thrombosis, even if distal or superficial, should be treated with anticoagulants for 3 months and patients with proximal DVT or any PE for 6 months [57]. There is some evidence that men who develop PE during cancer should remain on lifelong anticoagulation. Thus, the prudent emergency practitioner would be wise to consider thrombosis as a cause for disease in patients recently in remission. Patients with a history of cancer that is inactive and who develop thrombosis should be treated in accordance with guidelines recommended for a patient with unprovoked DVT (3–6 months) and PE (minimum of 6 months).

Table 24.4 Risk tool of Khorana for prediction of which patients undergoing chemotherapy will develop venous thromboembolism

Site of cancer	Risk score
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecological, bladder, testicular)	1
Prechemotherapy platelet count >350,000/μL	1
Hemoglobin <10 g/dL or red cell growth factors	1
Prechemotherapy white blood count >11,000/μL	1
Body mass index >35 kg/m^2	1

Thromboembolism Prophylaxis

Some malignancies confer an extraordinarily high risk of VTE, prompting the consideration to prescribe a prophylactic dose of anticoagulant [14]. Rivaroxaban was utilized in a double-blind, randomized trial of 841 high-risk, ambulatory, cancer patients, which demonstrated rivaroxaban did not significantly reduce the incidence of VTE or death from VTE over 180 days [58]. Conversely, several other studies have demonstrated some utility in VTE prophylaxis, such as in a study with 563 intermediate-to-high risk for VTE cancer patients (Khorana score ≥ 2, Table 24.4), using apixaban for VTE prophylaxis during chemotherapy. Primary outcomes were incidence of VTE in 180 days and major bleeding, and

Table 24.5 Contraindications to anticoagulation in the cancer patient [62]

Absolute contraindications
Active, major, serious, or potentially life-threatening bleeding that is not immediately reversible with medical or surgical therapies
Malignant hypertension, severe and uncontrolled
Liver failure leading to uncompensated coagulopathy (cirrhosis)
Severe platelet dysfunction, known bleeding diathesis, inherited bleeding disorder
Persistent thrombocytopenia (<20,000/μL)
High-risk invasive procedure needed (lumbar puncture)
TSA specific: concurrent use of P-glycoprotein or CYP3A4 inhibitor
Relative contraindications
Intracranial or spinal lesion at risk for bleeding
Active gastrointestinal bleed or risk for bleeding (ulceration)
Active but non-life-threatening bleeding (hematuria)
CNS bleeding in past 4 weeks
Recent high-risk procedure/intervention
Persistent thrombocytopenia (<50,000/μL)
Consider not starting anticoagulation
End of life, hospice patient
Asymptomatic thrombosis at high risk for bleeding
Patient refusal or against their wishes
Risk for nonadherence

apixaban was found to significantly reduce the rate of VTE compared to placebo, however, at an expense of increased major bleeding [59]. Similar other trials utilizing nadroparin and semuloparin have demonstrated reduction in thromboembolic events in cancer patients actively receiving chemotherapy [60, 61].

Given numerous recent studies exploring the efficacy and utility of VTE prophylaxis, a meta-analysis was completed of randomized controlled trials published over a 4-year period (2014–2018) [62]. The American Society of Clinical Oncologic (ASCO) recommends thromboprophylaxis with apixaban, rivaroxaban or LMWH for high-risk outpatients with cancer. Rivaroxaban and edoxaban have added as options for VTE treatment. Lastly, other recommendations have been made regarding VTE treatment in the setting of brain metastases, hospitalization prophylaxis, and prophylaxis in the setting of major cancer surgery. Concurrently, the emergency medicine physician must be aware of contraindications to therapy and these are listed in Table 24.5 [62]. Decisions to alter or discontinue VTE prophylaxis should occur in consultation with the patient's oncologist.

Incidental Diagnosis and Thrombophilia Workup

Patients will occasionally be diagnosed with PE discovered incidentally during routine imaging. This is often because of a CT scan of the chest performed with iodinated contrast for other reasons, such as staging of lung cancer or routine surveillance. The prognosis and treatment for these emboli are unchanged and confer the same risk to the patient as does symptomatic embolism [36]. All cancer patients with any confirmed venous thrombosis require systemic anticoagulation if they have no contraindications. Further, risk of recurrent VTE is significant despite anticoagulant treatment [63].

The thrombophilia workup adds only unnecessary cost to the care of the cancer patient [64]. In terms of treatment choices and duration, cancer dominates as the driver of decision-making regarding type and duration of anticoagulation, regardless of the patient's other genetic predisposition to thrombosis. Current guidelines do not support the testing of patients or their families for thrombophilia in the setting of a cancer-associated thrombus, including the "Choose Wisely" points issued by the American Society of Hematology [65]. Overtesting for inherited risk factors for VTE when not indicated lead to excess costs for patients and the health care system, and reductions in unnecessary testing can ultimately reduce health care costs [66].

Catheter-Associated Thrombosis

In 18 published studies of cancer patients with peripherally inserted central catheters, 6.8% (234/3430) were reported to experience deep venous thrombosis [67]. Intraluminal occlusions are best treated by interventional radiology or other specialists with access to and experience using fibrinolytic agents (e.g., Cathflo®) for this purpose. Extraluminal venous thrombosis (a form of DVT) can be treated by either removal of the catheter or anticoagulation with the catheter in place. In contrast to other sites of deep venous thrombosis, symptomatic PE occurs <5% of patients, but more than half experience total venous obstruction, which can lead to post-thrombotic syndrome and venous scarring with permanent stenosis [68]. Moreover, peripherally inserted central catheters (PICC lines) have a higher risk of thrombosis in cancer patients than central venous catheters [67]. PICC line-related DVT is highest within the first 2 weeks of placement, and smoking and high BMI significantly contribute to the rate of DVT; meanwhile, in a similar cohort, anticoagulation did not prevent thrombotic events [69, 70]. The decision to leave or remove the thrombosed catheter should be based primarily on the degree of swelling and pain, balanced against the need for the catheter and availability of alternative source of venous access, preferably determined in conjunction with the patient's oncologist. Regardless, PICCs can be safely and successfully utilized in nonhospitalized cancer patients for both chemotherapy and parental nutrition [71].

For indwelling lines used for active chemotherapy or other ongoing treatment, anticoagulation is often the best route. If the catheter can be removed, and the patient has trivial swelling and no pain, the author's preference for sub-

sequent treatment is a 7-day course of anticoagulation. Patients with visible swelling or pain should have 3 months of anticoagulation [29]. Prophylactic anticoagulation has shown disappointing results in both adults and children for prevention of catheter-associated thrombosis [72, 73].

Advanced Treatment

For all patients with massive PE, defined by either hypotension (systolic blood pressure <90 mmHg) or a 40 mmHg drop in systolic blood pressure (observed in the ED), clinical guidelines are aligned to recommend systemic fibrinolysis in the absence of contraindications [74, 75]. We recommend infusion of 15 mg of alteplase followed by 85 mg over 2 h. All patients should receive full-dose heparin anticoagulation (e.g., 5000 U unfractionated heparin bolus, followed by 16–18 U/kg/h infusion and PTT monitoring).

Patients with cancer have higher bleeding risk with standard anticoagulation and likely have higher bleeding risks with administration of fibrinolytic agents [76, 77]. Recent work suggests that a subpopulation of patients with DVT and PE will benefit from advanced therapies such as thrombolytics or catheter-based treatment [78, 79]. These patients fall primarily into two categories: DVT patients with large iliofemoral clot burden causing pain and leg swelling, and PE patients with right ventricular dysfunction, evidenced by an elevated troponin measurement (>99 percentile at a precision of 10% coefficient of variability), elevated brain natriuretic peptide (BNP >90 pg/mL), elevated pro-BNP (>900 pg/mL), or an echocardiogram demonstrating right ventricular hypokinesis or dilation, often defined as the right ventricular diameter larger than the left ventricular diameter (Table 24.6) [74]. Limited retrospective data exists for catheter-based treatment of either PE or DVT in cancer patients [80]. Regarding inferior vena caval filters in patients with PE who can be anticoagulated, no evidence has shown a clinically important net benefit for their insertion, and we do not recommend their use in any patient with PE who can be anticoagulated [81].

Table 24.6 Findings that suggest a worsened prognosis and may serve as indications for thrombolysis

Vital sign and physical examination abnormalities	Lab and imaging abnormalities
Systolic blood pressure <90 mmHg or a 40 mmHg drop from a known baseline blood pressure	Elevated cardiac BNP (>90 pg/mL) or pro-BNP (>900 pg/mL)
Hypoxemia (<92% at or near sea level) with respiratory distress	Elevated troponin or CK-MB
Altered mental status or delirium, usually seen as agitation, panic, and inattention	Right ventricular dilation with or without hypokinesis on echocardiography; a tricuspid annular plane systolic excursion (TAPSE) distance <16 mm; lobar or larger clot burden on CT together with RV > LV and evidence of contrast reflux

BNP brain natriuretic peptide, *CK* creatine kinase, *CT* computed tomography, *RV* right ventricle, *LV* Left ventricle

Patients with Absolute Contraindications to Anticoagulation

The treatment options are limited. An important intervention for these patients is to insert a vena caval filter as soon as possible [82]. With limited options for the patient in the presence of a strong contraindication to anticoagulation, such as active gastrointestinal bleeding, or recent glioblastoma surgery, physicians may be forced to consider treatments based upon case reports or hypothetical reasoning. These include inhaled nitric oxide (35 ppm by face mask or 50 ppm by nasal cannula) to reduce pulmonary vascular resistance and inhaled heparin localize anticoagulation in the lung vasculature [83]. Under fluoroscopic guidance, an interventional radiologist can place an infusion catheter through the body of the thrombus lodged in a proximal pulmonary artery and infuse 0.5 mg/h of alteplase with or without adjunctive ultrasonic (e.g., Ekosonic®), hydraulic (e.g., Angiojet®), or mechanical (e.g., rotating pigtail) thrombus disruption. No clinical trials have tested this method and the risk of hemorrhage remains unknown. Methods of clot extraction, including the use of the large bore Angiovac® device or open surgical thrombectomy, require that the patient be placed on an extracorporeal perfusion circuit with systemic anticoagulation.

Discontinuation of Treatment

One of the primary challenges of treating VTE in the cancer population is choosing a stop date for the desired therapy. In noncancer patients, anticoagulation may be continued for 3–6 months [84]. Given the prothrombic nature of cancer, the exact duration of anticoagulation treatment has no well-defined criteria. Instead, knowing that the risk of recurrence of thrombosis after discontinuation of anticoagulation exists, physicians must use their best judgment as to when to discuss discontinuation. Whenever possible, patients and families should be involved in the decision-making process, as at some point continuation of anticoagulation may offer no symptomatic benefit or improvement in the qualities of life [85, 86]. Ultimately, the decision to discontinue is best made through shared decision among all involved parties, especially as performance status declines and as death approaches.

VTE as First Manifestation of Cancer

Again, VTE in the setting of known cancer will not benefit from additional thrombophilia workup; however, a newly diagnosed, unprovoked VTE may be associated with underlying cancer [87]. One prospective study found that 3.3% of newly diagnosed VTE were the result of an underlying, undiagnosed malignancy, as compared to 0% of the provoked VTE. Furthermore, the presence of residual vein thrombosis in patients with unprovoked DVT who do not develop cancer within 3 months of the diagnosis of VTE is an independent predictor of subsequent overt malignancy [88]. Several other studies have demonstrated an association between idiopathic VTE and underlying undiagnosed cancer [89, 90].

Follow-Up

Discharge of patients for outpatient follow-up must be done in conjunction with an outpatient physician. This may either be the patient's primary care physician or oncologist. Determining if the VTE is primary or secondary may provoke physicians to perform additional testing to see if an underlying malignancy is present. As stated earlier, with the development of the target specific anticoagulants, routine anticoagulation monitoring in the form of "coumadin clinics" will become less prevalent, especially in view of the fact that warfarin is not recommended to treat active cancer. Thus, the role of the physician in evaluating and caring for the patient with blood clots will shift away from simple INR management and dosage adjustment, and instead focus on duration of therapy, prognosis, and quality of life. These skills are well within the purview of primary care physicians. Stopping criteria, while imperfect, can be used in a shared decision-making model to determine individual duration of anticoagulation [57].

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Gastroenterology

25

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Case Study

A 65-year-old male with 2-year history of diabetes presents to his local emergency department with a history of progressive anorexia, early satiety, and 2 days of jaundice. Work up revealed a bilirubin of 5.3 (high) and a CAT scan of the abdomen and pelvis showed a markedly dilated stomach that was fluid and food filled. A 3-cm solid enhancing mass was seen in the head of the pancreas resulting in upstream biliary obstruction, duodenal invasion, and pancreatic duct dilation. A nasogastric tube was placed in the emergency room to suction with prompt evacuation of 2.5 L of dark brown murky fluid and relief of many of his symptoms. Gastroenterology was consulted.

The following day, upper endoscopy revealed a high-grade ulcerated duodenal stricture at the apex of the duodenal bulb. The endoscope was unable to be advanced to the second portion of the duodenum due to the stricture. Endoscopic ultrasound was performed, and fine needle aspiration of the pancreatic mass was positive for malignancy per the rapid on site cytopathologist. A duodenal stent was placed traversing the stricture. After the enteral stent was allowed to expand over the next 2 days to facilitate endoscopic access to the major papilla, ERCP was performed with placement of a biliary stent across the malignant biliary stricture. Staging CT scans of the chest, abdomen, and pelvis were performed and demonstrated locally advanced pancreatic cancer. A multidisciplinary pancreatic oncologic team met and offered the patient neoadjuvant chemotherapy and staging CT scans to follow to assess for surgical resectability.

This case illustrates the use of advanced endoscopic techniques to diagnose and palliate symptoms of duodenal and biliary obstruction due to a new tumor diagnosis.

Introduction

In the past, gastroenterology's involvement in oncologic care centered on endoscopic tissue acquisition for malignant diagnoses. With technological advances in gastroenterology (GI), the field of interventional endoscopy has increasingly become married to cancer care from staging to surveillance to management of tumor or treatment-related emergencies. Oncologic emergencies in gastroenterology, much like that of other body systems, are related to the presence of cancer (the tumor itself or metastatic growth) or occur as a consequence of the treatments undertaken for cancer. In the GI tract, these include both structural derangements such as luminal or biliary obstruction as well as metabolic emergencies such as hepatic failure. In general, GI-related emergencies represent a minority of all oncologic emergencies, which are more often metabolic or hematologic. Many GI-related oncologic events require timely evaluation; however, for the most part, they are not imminently life threatening. These events will be the focus of this chapter. Some types of GI oncologic emergencies are insidious and develop gradually over time until a clinical threshold is achieved (e.g., gastric outlet obstruction, jaundice), whereas others may manifest over hours (e.g., cholangitis related to biliary obstruction).

In some patients, the devastating emergency is the first presentation of cancer itself. Given the increase in outpatient oncologic care in modern-day practice, early signs and symptoms of an evolving gastrointestinal emergency or urgency may be overlooked by patients and families. As with any emergency, early recognition and diagnosis are paramount to effective management. Early consultation with a gastroenterologist to help in diagnosis and management may

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Table 25.1 The most common oncologic emergencies in gastroenterology

Gastrointestinal hemorrhage
Luminal obstruction
Acute pancreatitis
Biliary obstruction/cholangitis
Hepatic decompensation
Dysfunction of enteral feeding devices

impact patient outcome, and thus, multidisciplinary care for complex oncologic patients serves the patient best. This chapter will examine the most common cancer-related gastrointestinal emergencies, discuss their diagnosis, and review their treatment (Table 25.1). Specifically, we will address gastrointestinal hemorrhage, enteral and biliary obstruction, acute pancreatitis, hepatic decompensation, and urgent issues related to enteral feeding.

Gastrointestinal Hemorrhage

Bleeding Related to Tumors

Neoplasia is considered an infrequent cause of upper gastrointestinal bleeding (UGIB), accounting for approximately 5% of all UGIB cases [1–4]. While oncologic patients are at risk for common causes of gastrointestinal bleeding (peptic ulcer disease, gastroduodenal erosions, esophagitis, etc.), those patients that have solid tumors of the gastrointestinal tract, or metastatic lesions that involve the GI mucosa, pose a bleeding threat from the esophagus to the anus. This risk is further compounded by the presence of neutropenia and thrombocytopenia, as well as the use of anticoagulation in the setting of tumor-related thromboembolic disease. These factors, as well as the innate characteristics of the tumor, can make endoscopic treatment of bleeding a significant management challenge. Additionally, cancer-related bleeding overall is a poor prognostic sign.

A large prospective study of over 3200 patients admitted with acute nonvariceal upper GI bleeding demonstrated that those patients with neoplasia had 2.5 times (95% CI, 1.32–4.46; $P < 0.0001$) the risk of death when compared to those who bled from benign conditions [1]. Of those with cancer ($n = 153$), the mortality rate was significantly higher in those with esophageal compared to cancer of the gastric cardia or gastric body (33% vs. 23.5% and 7.2%, respectively) [1].

Lesions in the esophagus (squamous cell carcinoma and adenocarcinoma), stomach (adenocarcinoma, gastrointestinal stromal tumors [GIST], lymphoma, carcinoid tumors, etc.), and proximal small bowel (adenocarcinoma, lymphoma, GIST, carcinoid tumors, etc.) are typically reached with a standard upper endoscope, while tumors in the jejunum and ileum often require the use of device-assisted enteroscopy, mainly in the form of single- and double-balloon enteroscopy or spiral enteroscopy. Colonic (adenocarcinoma, neuroendocrine [including carcinoid] tumors, etc.) and terminal ileal (adenocarcinoma, lymphoma) lesions are accessed via standard colonoscopy. Irrespective of the direction of endoscopic approach or the specific endoscope utilized, catheter-based devices (clips, injection needles, cautery devices) used to treat bleeding are advanced down the working channel of the endoscope and directed at the target lesion.

A variety of endoscopic techniques are available for the treatment of GI bleeding, and these modalities may also be applied to bleeding tumors although overall success rates of hemostasis are inferior compared to the endoscopic treatment of benign bleeding pathology. The main reason for the limited success of endoscopic therapy for tumor-related bleeding is that bleeding in such cases is not generally from a single exposed vessel (for which the majority of current endoscopic treatments are designed). Malignant bleeding tends to be diffuse mucosal oozing from numerous small microvessels, and therefore focal targeting of therapy is less effective due to the generally larger surface area involved.

The literature on the efficacy of endoscopic therapy for bleeding directly due to the primary or metastatic malignancy is sparse and is mainly based on case reports and series [5, 6]. Thermal therapies, including heater probe, bipolar electrocautery, and argon plasma coagulation (APC), are perhaps the most widely used modalities for tumor bleeding [7]. There have been a few case reports in the literature, but no trials comparing the efficacy of bipolar electrocautery and heater probe. A 1996 study by Savides and colleagues reported on the use of heater probe or bipolar electrocautery with or without epinephrine injection, in seven patients with focally oozing tumors. Initial hemostasis was achieved in all, but the 30-day rebleeding rate was 29%, similar to those not treated endoscopically [8]. Several studies have evaluated the use of neodymium-yttrium aluminum garnet (Nd:YAG) laser for tumor palliation in the GI tract [9–13]. Immediate hemostasis rates of 94% were achieved with the Nd:YAG laser for the emergent treatment of 18 patients with massive bleeding from esophageal and gastric cancer; however, rebleeding occurred in three of 17 patients with initial success, making laser therapy less suitable for definitive therapy [10].

Argon plasma coagulation (APC) is widely accepted as an effective modality for hemostasis as well as tissue fulguration and is readily available in most endoscopy suites and hospitals. It has generally replaced laser therapy due to its ease of use, low cost, and portability. The specific use of APC for palliation of upper GI tumor has not been well studied, with very few small case series [14–16] related to its use in esophagogastric or rectosigmoid cancers. Much of the lit-

erature related to APC in the setting of malignancy focuses on its use as a curative therapy for early-stage cancers (i.e., treatment of high-grade dysplasia in the setting of Barrett's esophagus, which has now been largely replaced by radiofrequency ablation or cryotherapy) or for decreasing tumor bulk to maintain luminal patency for palliation of dysphagia in esophageal cancer, which is discussed separately.

Spray cryotherapy is a newer endoscopic therapy that has been mainly used for the ablation of dysplasia associated with Barrett's esophagus (BE). Cryotherapy is a noncontact, targeted application of a cryogen (liquefied nitrogen or carbon dioxide) to destroy tissue through repeated freeze/thaw cycles [17]. Cryotherapy has been shown to completely eradicate high-grade dysplasia associated with BE in 97% of treated subjects [18]. This technology has also been applied to bleeding tumors with a single case report demonstrating hemostasis achieved in locally unresectable hemorrhagic esophageal cancer [19]. A major advantage of cryotherapy over other catheter-based endoscopic therapies for the treatment of bleeding from cancer is the surface area of coverage with cryotherapy treatment (several square centimeters) compared to the focal treatment effect (several square millimeters) of other probe-based endoscopic therapies (such as heater probe, bipolar electrocoagulation, hemostatic clips). It is expected that more literature will be published on its use in malignancy given its ease of use and wide surface area coverage.

A novel modality for the treatment of gastrointestinal bleeding is the use of hemostatic powders. These inorganic powders are designed to control active bleeding by two mechanisms: (1) adhering to the bleeding site and forming a mechanical barrier when in contact with blood, tissue, and the extracellular matrix; and (2) increasing local concentration of clotting factors while enhancing clot formation [20, 21]. Many of these products have been utilized in the military for temporizing battlefield-related injuries and show great hemostatic promise. There are currently three hemostatic powders available for endoscopic use, though only the TC-325 (Hemospray™, Cook Medical Inc., Winston-Salem, NC, USA) has FDA approval. Of all GI endoscopic therapies, hemostatic powders have thus far demonstrated the greatest potential for sustained hemostasis in malignancy. Several small case series demonstrate successful immediate and sustained hemostasis with hemostatic powders [22–25]. A recent pilot randomized control study also noted 90% immediate hemostasis rates and significantly lower rebleed rates compared to controls [26].

Mechanical methods of endoscopic hemostasis are in the form of hemoclips and are currently in use, with overall relatively poor results due to their focal targeted area of therapy. Once again, most tumor-related bleeding is diffuse mucosal hemorrhage rather than from a single exposed blood vessel. Hemostatic clips have most commonly been used for prevention of bleeding following endoscopic mucosal resection, but can be applied to neoplastic lesions. Cheng et al., reported two cases of hemostasis achieved by hemoclip placement on bleeding gastrointestinal stromal tumors [27]. Oftentimes, the bleeding tumor has several areas of active oozing, and mechanical disruption of the friable tumor with the use of a hemoclip may potentially worsen bleeding. Hemoclips are generally avoided in bleeding from tumors unless there is a focal targeted area of hemorrhage.

If endoscopic therapy fails to achieve hemostasis, angiographic evaluation by interventional radiology (IR) is generally the next step. While data on angiographic treatment of bleeding tumors is limited, angiography should be attempted as second-line therapy [28]. Access to the bleeding vessel may be achieved by selective catheterization in the distribution of the culprit vessel as evidenced by active contrast extravasation. Superselective embolization using microcoils or Gelfoam is highly successful in achieving hemostasis when the anatomy is favorable. However, given the nature of cancer-related bleeding, that is, diffuse mucosal hemorrhage from multiple microvessels, embolization of the feeding blood vessel may place the patient at risk for ischemia from collateral damage.

In those instances when both endoscopic and interventional radiology interventions are not successful in achieving hemostasis or not possible, targeted radiation therapy (RT) should be considered. Overall, RT plays a crucial role in the treatment of gastrointestinal malignancies and in the management of hemostasis. The effects of RT bleeding can be realized within a matter of days and a few fractions of treatment. In general, even though bleeding ceases, further treatment is undertaken to sustain a more durable response. RT causes damage to the intima of the blood vessels that supply the tumor, leading to capillary necrosis and thrombosis, and consequently hemostasis. This effect on tumor blood vessels as well as destruction of the tumor is the main mechanism by which RT is effective for hemostasis. Several retrospective studies on the role of RT on bleeding gastric cancers have demonstrated that palliative short-course RT is effective in hemostasis in 50–95% of cases [29].

In general, palliative surgical resection is the last option for definitive care of GI bleeding related to cancers and is associated with a poor prognosis [30, 31]. A comparison of elective and emergency presentation of gastric cancer in 291 patients reported that overall 2-year survival was less in those that presented with emergency complications requiring operative intervention (25% in emergency group versus 67% who presented electively) [31]. Surgical resection is only appropriate for surgically fit patients, and prior literature has suggested a mortality rate of 10% and morbidity rate of up to 30% in cancer patients [32–34]. Surgery indeed is effective in hemostasis; however, improvement in survival is extremely low at 6%, and the impact on the quality of life after palliative resection is not clear [33].

To date, there have been no prospective trials comparing endoscopic therapy, surgery or RT in the treatment of bleeding related to luminal tumor. Therefore, there is no clear answer as to which is the most effective treatment option. In general, the management approach is to enlist the least invasive method of hemostasis first, which may include the following sequence: endoscopy, then interventional radiology, then radiation therapy, then ultimately, surgery if necessary.

Bleeding as a Consequence of Treatment

Mallory-Weiss Tear. In patients receiving chemotherapy, nausea, vomiting, and retching are common. These symptoms place patients at risk for an upper GI bleeding related to a Mallory-Weiss tear, a mucosal injury at the gastroesophageal junction area that exposes a bleeding arterial vessel. Patients often present with hematemesis that may be clinically significant. This type of injury can produce significant bleeding especially in the setting of chemotherapy-induced thrombocytopenia. This condition can often be managed with endoscopic therapy alone with the use of electrocautery, epinephrine injection (for vasoconstriction and tamponade), or mechanical clips for hemostasis via upper endoscopy. If endoscopic therapy is unsuccessful in establishing hemostasis, IR-angiography is the next step for arterial embolization.

Radiation Proctitis. Radiation injury to the rectum and sigmoid may result from treatment of cancers of the prostate, cervix, rectum, anus, urinary bladder, and testes, occurring in up to 20% of these treated cancer patients. Endoscopic findings are mucosal ulceration, edema, erythema, bleeding, and telangiectasia from neovascularization (Fig. 25.1). It presents as persistent or intermittent hematochezia that may be associated with tenesmus or abdominal cramping and can be a significant source of GI blood loss. Acute radiation proctitis occurs either during or within 6 weeks of RT and is usually self-limited, while chronic radiation proctitis often occurs several months to years following RT [35]. Risk factors include the total surface area of exposure, method of delivery and cumulative radiation dose, with doses above 70 Gy resulting in long-term injury to the rectal mucosa [36]. Additional factors associated with the development of RT proctitis include prior GI or genitourinary surgery, endometriosis, diabetes, hypertension, collagen vascular disorders, and inflammatory bowel disease, all of which contribute to vascular compromise in the area [37]. Most cases of radiation proctitis are self-limiting and respond to medical therapy. In general, rates of radiation proctitis may be decreasing as RT techniques are improving to allow more targeted delivery of higher doses of radiation. While supportive care is typically offered for mild cases, patients who develop persistent outlet-type bleeding may benefit from targeted therapy. There is a paucity of well-designed trials comparing medical and endoscopic therapy, making it impossible to identify the most effective approach for the management of chronic radiation proctitis.

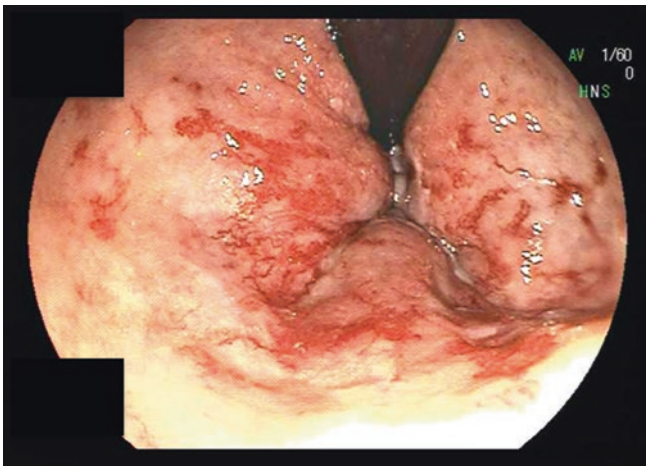

Fig. 25.1 Radiation proctitis. Endoscopic appearance of radiation proctitis, characterized by multiple telangiectasias in the rectum as seen on retroflexion in sigmoidoscopy. (Courtesy of Jeffrey L. Tokar, MD, Fox Chase Cancer Center, Philadelphia, Pennsylvania)

Treatment for radiation proctitis is medical therapy or endoscopic therapy. Medical therapy options include anti-inflammatory agents such as 5-aminosalicylic acid containing medications; antioxidants such as vitamin A, E, and C; sucralfate and short chain fatty acid enemas; and metronidazole and formalin therapy [38]. Kochhar and colleagues reported the use of sucralfate enemas in 26 patients, with durable remission of symptoms in a majority of patients with moderate-to-severe bleeding [39]. Several other reports have also demonstrated efficacy in improving symptoms of proctitis or proctosigmoiditis [39–41]. Given its overall low cost, minimal side-effect profile, and ease of administration, sucralfate topical therapy is a reasonable first step.

Endoscopic therapy with argon plasma coagulation (APC) is currently the first-line endoscopic modality for treatment of bleeding associated with radiation proctitis. It is easy to use, effective, widely available, safe, and relatively inexpensive. The goal of endoscopic therapy to is obliterate the telangiectasias. APC provides a predictable, noncontact, uniform, limited depth of coagulation (0.5–3 mm) to the target tissue, resulting in lower risks of perforation, stricture, and fistula formation [42, 43]. Studies have also demonstrated sustained remission of bleeding in patients with severe radiation proctitis (90% in a mean follow-up of 18 months) [44]. Typically, more than one session of APC

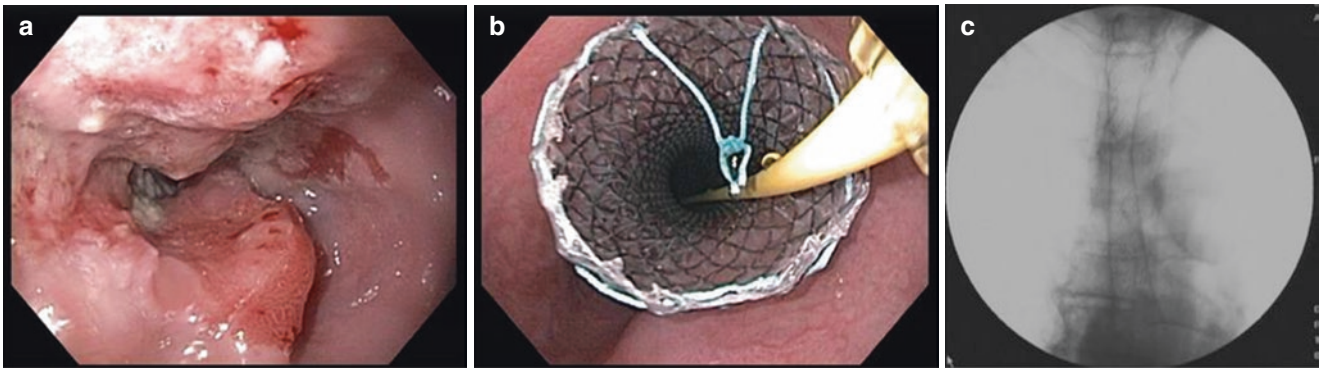

Fig. 25.2 Palliation of duodenal (**a**) and biliary obstruction (**a**, **b**) from pancreatic cancer. (Courtesy of Vinay Chandrasekhara, MD, University of Pennsylvania, Philadelphia, PA, and Kaveh Sharzehi, MD, Oregon Health & Science University). Two example fluoroscopic images of dual duodenal and biliary stenting (**a**, **b**)

therapy is required, with durable hemostasis achieved after three sessions [38, 45].

Other endoscopic treatments include radio-frequency ablation and cryotherapy [46]. Both these therapies have the advantage of allowing a broader field of treatment than the focal therapy of APC. Initial studies have demonstrated high rates of hemostasis (>90%) as well as minimal to no side effects (up to 19 months of follow-up) with both RFA and cryotherapy [47–49], though all studies are small. RFA has the benefit of inducing neosquamous epithelialization that may prevent recurrence of symptoms, but this has yet to be studied formally [43]. Hyperbaric oxygen therapy (HBOT) is currently utilized for the treatment of radiation proctitis in those patients who have failed more conventional medical or endoscopic techniques. It involves inhalation of 100% oxygen, delivered daily for weeks in a full body chamber with increased atmospheric pressure. It has been shown to be 89% effective with minimal morbidity with overall good compliance with treatment [50]. However, this therapy is not widely available and is often associated with wound care centers.

Luminal Obstruction

Patients with GI malignancies are at risk for obstruction of the GI tract, which is the most common surgical emergency encountered in the cancer patient [51]. Obstruction is characterized by poor oral intake due to nausea, vomiting, abdominal pain, and paucity of stool or flatus passage. Abdominal X-rays or CT scans may reveal air-fluid levels and a transition point indicating the site of obstruction. Initial management is conservative, with bowel rest, intravenous fluids, antiemetics, electrolyte repletion, and nasogastric (NG) tube placement for decompression. In general, the majority of noncancer-related bowel obstructions related to adhesions resolve in this conservative approach.

Malignant obstructions of the esophagus, stomach, duodenum, and colon can be alleviated by placing a self-expanding metal stent (SEMS) via endoscopy. Stents are placed with endoscopic and fluoroscopic guidance and are generally effective at maintaining patency in this setting (Fig. 25.2). SEMS has been shown to be a safe and effective means of maintaining esophageal patency in the setting of malignancy and the procedure has a very high technical success rate. Stent migration is the most common complication, with widely varying rates. While patients should be made aware of this potential in the informed consent process, the advent of stents with antimigration struts and endoscopic suturing devices, this risk has been reduced significantly [52, 53]. Post-procedure pain can be quite significant and is common, but often resolves after 48–72 h, with oral analgesia as support. Other considerations are the management of the induced acid reflux of the gastroesophageal junction that is bridged with the stent. As such, patients with esophageal stents are generally provided with a twice daily proton pump inhibitor (PPI) as well as instructed to sleep at a 45° angle indefinitely. The decision to place a SEMS for esophageal cancer is institution dependent and best made in a multidisciplinary setting. In some cases, surgeons prefer not to have an esophageal stent in situ if the patient is a candidate for an esophagectomy and instead prefer to provide nutrition via a surgically placed jejunostomy tube (at which time, surgical ischemic conditioning of the future gastric conduit can be performed). Esophageal stents, in this instance, are reserved for palliative cases only. Alternatively, some practices routinely place SEMS for obstructing esophageal cancer to aid in nutritional improvement prior to neoadjuvant therapy and surgery.

Gastroduodenal stenting for malignant obstruction of gastric, duodenal, or pancreatobiliary cancers has technical success rates of 90–95% according to multicenter retrospective studies [54], resulting in the ability to tolerate an enteral diet. Reintervention rates are low (only 5%), providing evidence

that enteral stents achieve excellent palliation. Overall prognosis should be considered prior to palliative luminal stenting. If patient life expectancy is anticipated to exceed 6 months, a more durable approach such as a surgical bypass (gastrojejunostomy) should be employed. While generally well tolerated, the main complications of gastroduodenal stenting include stent migration, perforation, and stent obstruction by tumor or food. These obstructions can typically be resolved endoscopically by placing a stent within the originally placed stent [55–57]. GI has witnessed multiple endoscopic advances with the use of endoscopic ultrasound and one of them has been the endoscopic gastrojejunostomy in which a lumen apposing metal stent is used to create a stable fistula between the stomach and jejunum. This novel technique is being refined currently but shows promise to potentially avoid surgeries in patients with advanced cancers [58–60].

Simultaneous biliary and gastroduodenal stenting is performed relatively commonly and has been shown to be a safe and effective means of palliation [61, 62] (Fig. 25.3). An additional consideration is that luminal stenting may not be effective for infiltrative-type gastric cancers in which motility is significantly compromised due to tumor (i.e., linitis plastica), rather than a true obstruction.

Finally, colonic stents have been used in the setting of colonic obstruction for palliation and also for colonic decompression prior to surgical intervention (so-called bridge to surgery). Once again, similar to other luminal stenting, technical (>92%) and clinical success rates (>89%) are high, and adverse rates are generally low, although some studies raise concerns about perforation [63–65]. There are multiple studies evaluating the role of colonic stents with respect to bridge to surgery or allowing for a one-step surgery (i.e., primary anastomosis versus an ostomy with subsequent takedown and anastomosis). Overall, results from the available literature are highly variable largely due to multiple small studies, lack of homogeneity in patient populations, as well as definitions of success and treatments. The most recent meta-analysis of eight RCTs and 497 patients in the surgical literature shows that stent as a bridge to surgery over emergency surgery for left-sided malignant colonic obstruction was associated with lower 60-day morbidity and lower rates of stoma formation; however, 30-day mortality rates are no different than surgery [66].

For surgically unresectable disease, with a life expectancy <6 months, colonic stenting is the treatment of choice [67, 68]. In potentially curable disease, colonic stents should only be considered when surgical intervention is anticipated to shortly follow stent placement. A multidisciplinary discussion between the performing gastroenterologist, the colorectal surgeon, and oncologist is warranted to optimize patient outcomes, given the lack of clear data in this area [69].

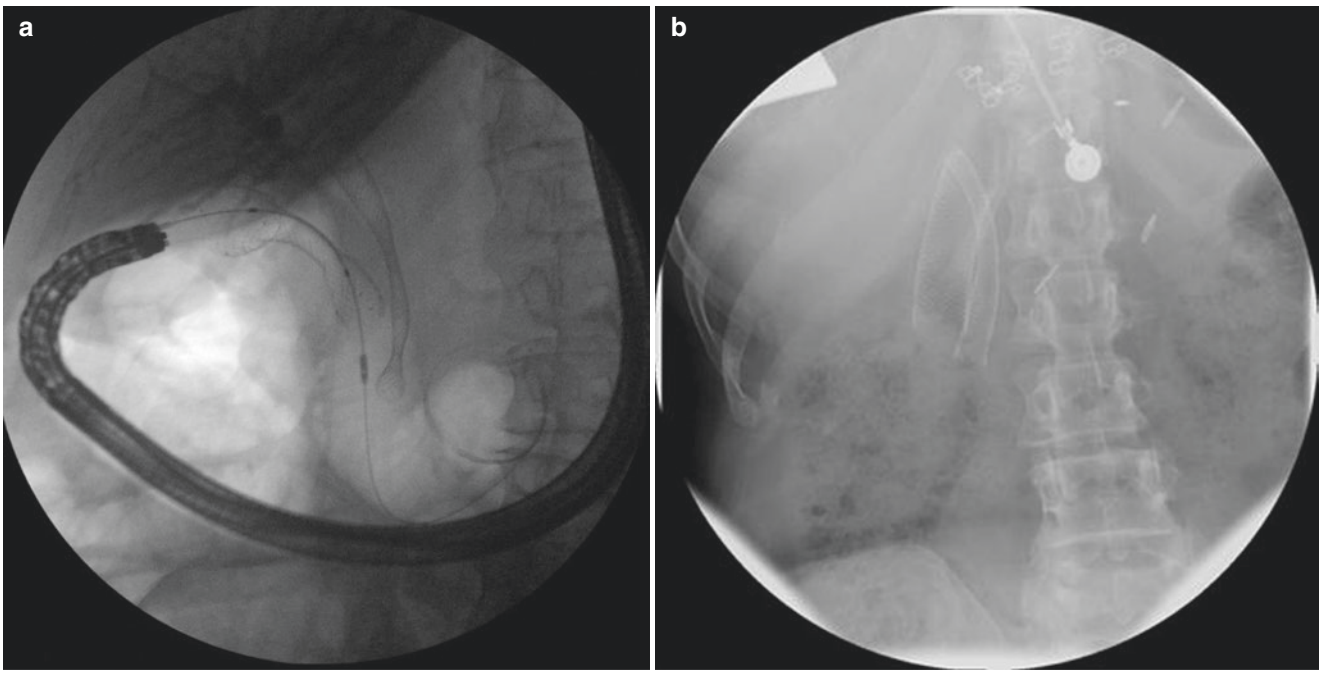

Fig. 25.3 Palliation of duodenal (**a**) and biliary obstruction (**a**, **b**) from pancreatic cancer. (Courtesy of Vinay Chandrasekhara, MD, University of Pennsylvania, Philadelphia, PA, and Kaveh Sharzehi, MD, Oregon Health & Science University). Two example fluoroscopic images of dual duodenal and biliary stenting (**a**, **b**)

Acute Pancreatitis

In patients with cancer, acute pancreatitis may occur as a result of pancreatic duct obstruction from tumor or as a result of chemotherapeutic agents. The diagnosis of acute pancreatitis is established by two of the following: clinical symptoms of abdominal pain; elevation of serum pancreatic enzymes greater than three times the upper limit of normal; and imaging studies documenting active pancreatic inflammation (CT or MRI with or without intravenous contrast). Mechanical obstruction of the main pancreatic duct or its branches is one of the etiologies of acute pancreatitis. While the most common reason for such an obstruction is gallstone disease, pancreatic neoplasms are recognized as an important, albeit more rare, cause of acute pancreatitis [70]. The risk of pancreatic adenocarcinoma after a single episode of acute pancreatitis is increased, with diagnosis that is often delayed for up to 2 years [71]. Age greater than 50 years, a history of smoking, weight loss of 10 lb or greater, serum bilirubin of 2 mg/dL, or alkaline phosphatase level greater than 165 U/mL, as well as radiologic findings of distal pancreatic atrophy or mass had statistically significant association with the subsequent diagnosis of pancreatic adenocarcinoma on follow-up [72]. Pancreatic neuroendocrine tumors are an uncommon cause of acute pancreatitis, but also should be included in the differential diagnosis of acute pancreatitis, especially in patients older than 40 years in whom the etiology of acute pancreatitis is not clear [73].

Acute pancreatitis can sometimes be the first presentation of primary pancreatic or ampullary neoplasms or metastatic disease to the pancreas [74, 75], the latter of which has been described in patients with cancers of the lung, kidney, bile duct, and melanoma [76]. Malignancy-associated hypercalcemia may also be the cause of acute pancreatitis [77]. The risk of primary pancreatic cancer is significantly increased in patients with hereditary pancreatitis due to genetic mutations; the risk of pancreatic adenocarcinoma in these individuals is as high as 54% by age of 75 years [78].

Acute pancreatitis may also develop in patients undergoing antineoplastic chemotherapy. While in general, less than 2% of acute pancreatitis is drug induced, the development of acute pancreatitis has been infrequently associated with antineoplastic chemotherapy. While it is often impossible to definitively conclude that a particular drug is the etiology of pancreatitis without rechallenge, multiple cases of chemotherapy-induced pancreatitis have been reported, including with capecitabine, paclitaxel, bortezomib, vinorelbine, and ifosfamide. Rechallenge was not attempted in many of the reported cases [79]. Tamoxifen may act through induction of hypertriglyceridemia to induce pancreatitis [80]. It is important to recognize that patients receiving chemotherapy can develop acute pancreatitis independent of their tumor or therapy for malignancy due to common etiologies such as gallstone disease or alcohol.

The management of patients with acute pancreatitis involves administration of aggressive intravenous fluid hydration, analgesia, and bowel rest. Aggressive hydration is defined as 250–500 mL/h (unless cardiovascular or renal indications dictate otherwise), with close observation of urine output and adjustment of hydration as needed, with the goals of decreasing blood urea nitrogen [81]. Early effective management of acute pancreatitis is critical to prevent multiorgan failure (renal failure, hypotension, respiratory compromise, and cardiovascular collapse) that can ensue as a result of the systemic inflammatory response syndrome [82, 83].

Inadequate early hydration may lead to any of these devastating consequences and is one of the most common clinical pitfalls in the management of acute pancreatitis. Furthermore, strict bowel rest (nil per os status, NPO) until patients are pain-free to limit pancreatic stimulation is a hallmark of initial management. The vast majority of patients have a mild course with inpatient admission for <5–7 days. In those cases in which the patient's clinical course dictates prolonged NPO status for more than 3–5 days, supplemental nutrition is indicated, preferably by enteral route with NG or nasojejunal (NJ) feeding. The optimal strategy is usually to allow the patient to consume nutrition per os; however, many patients are unable to meet the metabolic demands via only PO intake, and thus enteral nutritional supplementation should be instituted. In patients with acute pancreatitis, enteral nutrition significantly reduced mortality, multiple organ failure, systemic infections, and the need for operative interventions compared to those who received TPN. This was demonstrated in a meta-analysis of eight randomized controlled trials [84].

Patients who develop complications as a result of acute pancreatitis such as acute pancreatic fluid collections, pancreatic necrosis, or pseudocyst warrant a multidisciplinary discussion with gastroenterologists, including interventional endoscopists and pancreatic surgeons to optimize management of such complications.

Biliary Obstruction

Malignant obstruction of the biliary tree can arise from primary tumors of the bile duct (intrahepatic or extrahepatic cholangiocarcinomas) or from extrinsic compression and/or invasion of the bile duct by pancreatic, ampullary, or duodenal cancers and lymphadenopathy (peripancreatic or portal lymph nodes), or from metastatic spread to the biliary tree or liver. Biliary obstruction manifests as jaundice, acholic stool, dark urine, pruritus, abdominal pain, nausea, and weight loss. Cholangitis may occur as a result of biliary stasis and

subsequent infection; however, in general, in the absence of prior biliary intervention or choledocholithiasis, ascending bacterial cholangitis is uncommon in patients with malignant biliary obstruction.

Biliary obstruction is diagnosed by abnormalities in serum bilirubin, alkaline phosphatase, and liver transaminases, as well as imaging (ultrasound, CT, MRI) showing evidence of obstruction such as biliary dilation proximal to the site of obstruction. Once established, it is important to triage the urgency of biliary decompression. Patients with asymptomatic jaundice do not require biliary decompression unless their hyperbilirubinemia interferes with chemotherapy (i.e., some chemotherapeutic regimens require a normal bilirubin). Patients with intolerable jaundice or pruritus or poor nutritional status as a result of hyperbilirubinemia should have elective biliary decompression. Pruritus associated with hyperbilirubinemia can be debilitating and has been managed with antihistamines, corticosteroids, cholestyramine, and other medications with only limited success, thus relief of obstruction is the mainstay of treatment. Those patients with signs and symptoms of acute cholangitis require urgent drainage and intravenous antibiotics.

Biliary decompression can be accomplished by endoscopic (endoscopic retrograde cholangiopancreatography, [ERCP]) (Fig. 25.4), percutaneous (interventional radiology), or surgical means. With the development and advances in endoscopic and percutaneous drainage procedures, surgical decompression is rarely utilized in modern clinical practice.

Endoscopic and percutaneous biliary drainage procedures have their individual risks and benefits. Common risks to both procedures include infection, stent occlusion, or migration. Endoscopic drainage via ERCP is considered relatively noninvasive, highly successful, and well tolerated. However, it carries risks associated with bleeding specifically from the biliary sphincterotomy site, intestinal perforation, and procedure-related pancreatitis (generally 3–10%) [85]. Percutaneous transhepatic cholangiography (PTC) eliminates the potential for acute pancreatitis and intestinal perforation and requires less sedation than ERCP. It is highly successful especially in high-volume centers through, may be challenging in cases where there is no significant intrahepatic biliary dilation to serve as a target. This means biliary drainage may be necessary in the setting of gastroduodenal obstruction, although new endoscopic ultrasound-guided adjunct techniques allow for biliary drainage in this setting (i.e., choledochoduodenostomy). Percutaneous biliary drains can be replaced and exchanged with relative ease. Nevertheless, percutaneous biliary drainage does leave the patient with an external drain which may impact their quality of life, while endoscopic drainage obviates the need for external catheter drainage.

ERCP-placed stents can be plastic or metal (self-expandable metal stents, SEMSs). The advantage of plastic stents is their low cost and relative ease of removal, if needed, at the time of surgery. Plastic stents, however, have shorter life span due to their smaller diameter (maximum diameter of plastic stent is 12 French, 4 mm) and may not maintain patency long enough to allow for neoadjuvant chemoradiotherapy in cases of pancreatic adenocarcinoma. Up to 55% of patients with ERCP-placed biliary plastic stents for malignant obstruction from pancreatic cancer require additional ERCP intervention for biliary obstruction or cholangitis related to stent occlusion [86]. Biliary SEMS do not adversely affect surgical outcomes and are preferable for more durable stenting, however are more expensive upfront. Decision analysis studies have not shown plastic stents to be more cost effective for pancreatic cancer [87, 88].

While biliary metal stents have been shown to be superior to plastic stents for decompression caused by pancreatic adenocarcinoma by maintaining patency longer, stent occlusion may still develop. In a multicenter study of 241 patients treated with metal stents as part of preoperative protocol, 5.8% of patients developed stent occlusion with a median time to occlusion of 6.6 months (range 1–20 months) [89]. Mechanisms of metal and plastic stent malfunction differ.

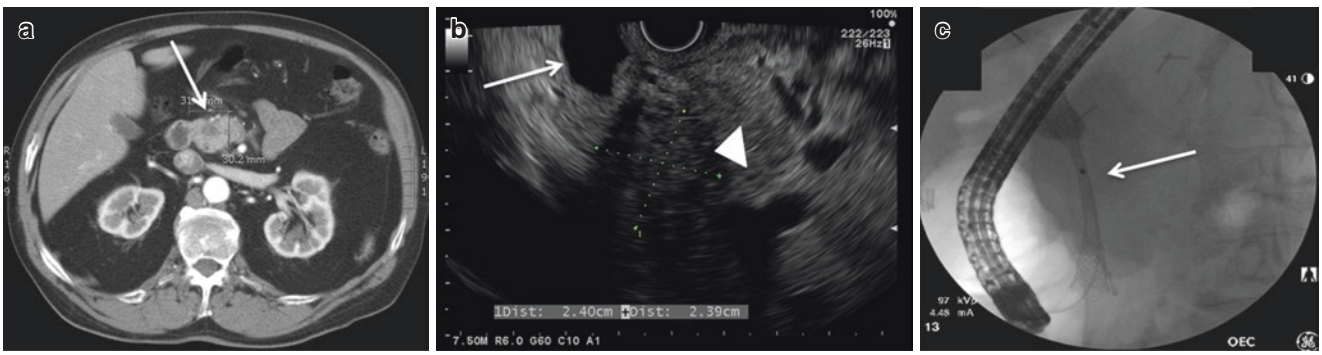

Fig. 25.4 Obstructing pancreatic adenocarcinoma. (**a**) A 2.5-cm ill-defined lesion in the pancreatic head on CT scan; (**b**) pancreatic head mass (*arrowhead*) resulting in biliary obstruction and dilated common bile duct (*arrow*) on endoscopic ultrasound; and (**c**) tight fluoroscopic waist within ERCP-placed self-expanding biliary metal stent for obstructing pancreatic head mass

Plastic stent may occlude due to formation of bacterial biofilm and sludge formation, or they may migrate proximally or distally and no longer span the obstructing biliary stricture. There may be tumor overgrowth covering the proximal end of the stent. Covered metal stents may have similar mechanisms for occlusion. Uncovered metal stents are less likely to migrate; however, there may be tumor or benign reactive tissue ingrowth, in addition to biofilm and sludge formation.

Patients with occluded biliary stents or percutaneous catheters may present with recurrence of their original symptoms that led to interventions, as well as jaundice, fever, chills, and abdominal pain. Intermittent obstruction due to sludge and stones is possible. Imaging studies may show biliary dilation. Lack of pneumobilia (an expected finding in patients with patent biliary stents) may be a radiologic clue to biliary obstruction, but it is neither a specific nor sensitive finding.

The acute management of biliary obstruction with cholangitis in patients with malignancy is not different from patients with benign disease and involves management of sepsis with intravenous fluids, broad-spectrum antibiotics, and prompt establishment of biliary drainage via endoscopic or percutaneous methods. Endoscopic management options of occluded stents include removal of the occluded stent and placement of new covered or uncovered metal stent or plastic stent. Percutaneous catheter exchange in patients with prior PTC is the treatment of choice for acute cholangitis.

Management of these complicated patients necessitates a multidisciplinary team with input from medical, radiation, and surgical oncologists, the patient's primary care physician, interventional radiologists, and gastroenterologists to determine the optimal management strategy.

Hepatic Decompensation

Fulminant Hepatic Failure

Fulminant hepatic failure due to malignant infiltration of the liver is rare, but has been reported in case studies in the literature [90, 91]. These case reports have centered on diffuse infiltration by tumor cells (lymphoma and infiltrative carcinoma) rather than numerous hepatic metastases and could not be distinguished on cross-sectional imaging. Though it is a rare complication of metastatic liver disease, it carries a high mortality. Many chemotherapeutic agents may have hepatotoxic manifestations and thus the selection of the appropriate antineoplastic regimen must take into account the patient's baseline liver chemistries and associated comorbidities. Polypharmacy which many oncologic patients are the victims of is also an additional cause of abnormal liver chemistries. Most often, drug induced liver injury is self-limited (possibly limited to abnormal liver chemistries) and can be reversed with removal of the offending agent; however in rare cases, it may lead to fulminant hepatic failure with a decline in synthetic liver function.

In the setting of fulminant hepatic failure, patients usually present with jaundice, altered mental status or bleeding. The etiology is due to replacement or destruction of hepatocytes with tumor resulting in the compromised liver synthetic function. As a result, there is decreased synthesis of albumin and oncotic proteins which promote the development of ascites, decreased conjugation of bilirubin resulting in jaundice, or obstruction of intrahepatic ducts from tumor resulting in jaundice, bleeding due to elevations in the prothrombin/international normalized ratio (INR) due to derangements in the synthesis of key clotting factors, and eventually decreased ability of the liver to process toxins resulting in encephalopathy. Cerebral edema may develop in patients with acute liver failure leading to increased intracranial pressure and risk of subsequent herniation. The early recognition of acute liver failure is critical given its overall dismal prognosis if left untreated. In cases in which the etiology is nonmalignant, lifesaving measures such as orthotopic liver transplantation should be considered. Clearly, when malignancy is the underlying etiology, recognition of hepatic decompensation is a sign of terminal prognosis.

Laboratory evaluation initially should include liver enzymes including AST, ALT, alkaline phosphatase, GGT, total and direct bilirubin, albumin, prothrombin time/INR, serum chemistries, ammonia level, and viral serological tests. Cross-sectional imaging may show diffuse hepatic involvement by tumor resulting in loss of hepatic reserve (Fig. 25.5). It is important to exclude a secondary etiology to liver dysfunction that may be at play and cause the sudden

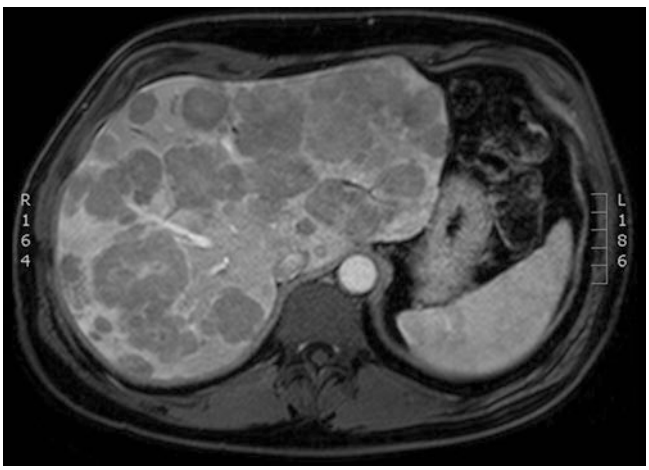

Fig. 25.5 Innumerable intrahepatic masses due to metastatic colorectal cancer resulting in jaundice and compromised synthetic liver function. (Courtesy of Alice Fung, MD, Oregon Health & Science University)

imbalance in liver synthetic function. Thus, formal hepatology consultation is appropriate. Additionally, it is important to exclude extrahepatic biliary obstruction as an underlying etiology for jaundice as therapy for biliary obstruction may lower the patient's bilirubin enough to allow for further oncologic treatment. In this vein, cross-sectional imaging (CAT scan of the abdomen or preferably MRI/MRCP) and consultation with gastroenterology and interventional radiology may benefit the patient. In general, progressive malignant liver dysfunction leads to hospice. Nonetheless, it is important to exclude reversible contributing illness to a patient's declining hepatic function.

Ascites

Ascites, defined as free intra-abdominal fluid accumulation, may be a result of malignancy with and without liver involvement. Ascites may be detected due to the presence of bloating, abdominal distention, and dullness to abdominal percussion. Abdominal ultrasound may be required to determine with certainty that fluid is present within the abdomen. Breast, lung, colon, and pancreatic primary malignancies are most commonly complicated by ascites [92]. In addition, significant intrahepatic tumor burden may result in liver dysfunction and subsequent ascites.

While there are many possible etiologies of ascites including cirrhosis, Budd-Chiari syndrome, pancreatitis, congestive heart failure, etc., we will focus on malignancy-related ascites. The serum-ascites albumin gradient (SAAG) has been used to categorize ascites; it is able to differentiate portal hypertensive ascites vs. nonportal hypertension-related ascites with a diagnostic accuracy of 97% [93, 94]. In a patient with new ascites, a diagnostic paracentesis is performed in order to calculate this gradient and help identify the etiology. The pathophysiology of malignant ascites is not related to portal hypertension, and thus these patients have a SAAG <1.1 g/dL. There are several pathophysiologic mechanisms of malignant ascites including lymphatic obstruction by lymphoma or mass, low serum oncotic pressure due to various causes (including massive liver metastases with liver dysfunction), and exudation of proteinaceous fluid from tumor cells that line the peritoneum in patients with peritoneal carcinomatosis [92].

Unlike portal hypertension-related ascites in which the underlying pathophysiology involves a complex interplay of splanchnic and systemic vascular resistance coupled with sodium and water retention which in general responds to dietary sodium restriction, diuretics (such as furosemide or spironolactone), or intravascular volume expansion (intravenous albumin), the mainstay of the management of malignant ascites is large-volume paracentesis for symptomatic relief. This can be arranged as an outpatient via ultrasound guidance with interventional radiology or with gastroenterology. The timing and frequency of paracenteses are dictated by patient symptoms. In general, peritoneal catheters are avoided in these patients given the potential for loss of protein and hydration as well as potential to seed the catheter track. In patients with malignancy ascites related to ovarian cancer, tumor debulking and chemotherapy may be effective in ascites management (Sugarbaker technique).

Urgent Issues Related to Enteral Feeding Devices

Many patients with cancer battle with issues related to malnutrition. This is due to the prolonged negative balance of protein and energy below metabolic requirements that result from the tumor itself or intensity of treatments. As such, cancer patients may require supplemental enteral feeding via nasoenteral tubes, gastrostomy, or jejunostomy feeding devices. The type of enteral access is usually decided upon based on the length of anticipated need. Nasoenteric tubes are commonly used and have the benefit of relative ease of placement. Such tubes are utilized when the feeding is predicted to be approximately less than 30–45 days. Dislodgement of nasoenteric tubes is usually not of major concern as they are easily replaced and dislodgement can be prevented by the use of a nasal bridle device [95–97].

When long-term enteral access devices are needed, gastrostomy or jejunostomy tubes are the most common methods. Such devices may be placed by endoscopic (gastroenterology), percutaneous (interventional radiology), or surgical means. Once placed, it is recommended that these devices should not be removed for at least 6 weeks to allow the enterocutaneous fistula to mature prior to intentional removal. The patient should be made aware that once removed, the track can take up to 2 weeks to close and to expect some leakage during this time frame.

Enteral access replacement may be urgently needed in cases of unintentional dislodgement in order to prevent closure of the enterocutaneous fistula. If dislodgement occurs within 14 days of insertion, this track may not be mature, and "blind" reinsertion of a tube via the fistula should not be attempted to avoid erroneous placement of the enteral device into the peritoneal cavity [98]. The patient should be advised to call the provider who initially inserted the enteral device to arrange for reinsertion or present to the emergency department. In cases where the track is mature (>6 weeks from placement) and the device is dislodged, a temporary tube

such as a Foley balloon catheter can be inserted in the track to maintain patency until the appropriate replacement device can be inserted and secured. This can be done at the bedside in any emergency. By directly addressing the dislodged tube in a timely manner, the clinician may be able to avoid the need for an endoscopic, interventional radiology, or surgical replacement procedure.

Summary

GI-related oncologic emergencies represent a small proportion of all oncologic emergencies and those herein discussed include GI bleeding, luminal and biliary obstruction, acute pancreatitis, hepatic decompensation, and dislodgement of enteral devices. These disorders require early recognition allowing clinicians, patients, and families to be aware of these possibilities and aid in early identification of such emergencies. A multidisciplinary approach to such patients and conditions, including consultation with oncologic, radiation oncologic, surgery, primary care, and gastroenterology to assist in management (which may include a therapeutic GI procedure), is likely to lead to optimal patient outcomes.

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The Acute Abdomen

26

Linda Ferrari and Alessandro Fichera

Case Study

History present illness: A 57-year-old woman presenting to the emergency department for persistent left upper quadrant pain, nausea, and weight loss. Pain is constant in nature over the past 5 days. She has been having regular bowel movements, formed stools without blood or mucus.

Laboratory values: Hb 107 g/L (120–150 g/L), CRP 272 mg/L (0–4 mg/L).

Abdominal radiograph: No features of intestinal obstruction or perforation

CT chest, abdomen, and pelvis: Highly suspicious wall thickening involving the distal transverse colon/splenic flexure with extramural involvement of the left colic and inferior mesenteric vein. Regional lymph nodes are enlarged. There is an associated collection measuring approximately 4.8 × 4.1 cm which is suggestive of focal tumor perforation. There is surrounding inflammatory changes and it is difficult to exclude associated peritoneal involvement. Such collection is abutting the gastric wall with edematous wall thickening and a likely perforation into the gastric lumen. No definite distant metastatic disease.

Past medical history: Seven years before, patient had right breast invasive cancer. She underwent mastectomy with implant-based reconstruction, axillary clearance, chemoradiation therapy, and adjuvant endocrine treatment with Letrozole (aromatase inhibitor).

Hospital course: The patient underwent upper endoscopy which showed a lesion within the stomach, biopsy showing inflammatory tissue and a colonoscopy which showed a transverse colon lesion consistent with invasive adenocarcinoma. The patient was then discharged awaiting colorectal multidisciplinary team discussion and readmitted 2 days later for nausea and inability to tolerate oral intake. An extended right hemicolectomy and en-block partial gastrectomy was recommended and performed as a combined procedure involving an upper and lower gastrointestinal surgeons. The anastomosis was protected with a diverting loop ileostomy.

Key message: Patients with cancer involvement of multiple organs should be management in the context of a multidisciplinary team to optimize outcome.

Small Bowel Obstruction

Small bowel obstruction (SBO) is a common condition responsible for over 300,000 annual hospital admissions in the United States [1], associated with 10% of mortality rate and significant morbidities among survivors [2]. Small bowel obstruction occurs when the flow of contents through the intestines is interrupted. Simple SBO may lead to intestinal dilation, hypersecretion, bacterial overgrowth, and vascular impairment. Closed loop obstruction may immediately compromise mesenteric blood supply leading to ischemia, necrosis, and perforation with subsequent peritonitis.

Patients with SBO are often unable to tolerate oral intake for several days and they should be considered as patients having acute intestinal failure, which has been defined by the European Society of Coloproctology as "the reduction of function below the minimum necessary for the absorption of macronutrients and/or fluids and electrolytes, such that intravenous supplementation is required to maintain health and/or growth" [3].

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The most frequent cause of small bowel obstruction is abdominal adhesions following previous surgeries which account for approximately 60–70%, followed by hernia in approximately 15% of the cases, including incisional, inguinal, and parastomal [4]. Cancer has been estimated to be the third cause of small bowel obstruction, with approximately 8–10% cases. In the National Audit for Small Bowel Obstruction (NASBO) [5], 205 (8.4%) out of 2431 patients had cancer as the primary cause of small bowel obstruction. Of those, disseminated intra-abdominal malignancies are the most common cause responsible for 70% of cancer cases, followed by right colon cancer (24.4%), while primary tumors of the small bowel represent only 4.9%.

Malignant bowel obstruction (MaSBO) has been defined "as definitive diagnosis of intestinal obstruction distal to the ligament of Treitz and the presence of incurable intra-abdominal malignancy or extraabdominal primary (melanoma, breast, and lung) with known intraperitoneal metastases" [6]. MaSBO is a life-threatening complication of intraabdominal cancer, with an incidence between 5% and 51% in patients with ovarian carcinoma and between 10% and 28% in patients with gastrointestinal malignancies [7]. Different mechanisms are responsible for the occlusion, such as a cancer obstructing the lumen, impaired intestinal motility, medication-related (i.e., opioid analgesics) and radiation therapy complications or sequelae [8].

Obstruction in a patient with previous history of cancer or with a recent diagnosis may also be secondary to benign causes including fibrosis or stricture, postoperative adhesions or ileus, medication-related dysmotility or treatment-related edema. Generally, MaSBO of the small bowel is more likely to be multifocal and extrinsic; the most common cancers leading to this are metastatic ovarian and colorectal adenocarcinoma with peritoneal implants, direct invasion, or carcinomatosis [8]. Other causes of SBO may include an obstructing mass which can be extrinsic and compressing the bowel (e.g., carcinomatosis with implants) or less frequently intrinsic (e.g., small bowel adenocarcinoma, lymphoma).

Goals of therapy for SBO include relieving symptoms of nausea, vomiting, and pain, allowing oral intake. These goals, in the case of MaSBO or primary small bowel cancer, should be weighed against the high morbidity and mortality rate in this cohort of patients [5, 9–11] and palliative care considerations should be entertained. The goals for treatment should be individualized for each patient especially for those facing end-of-life decisions.

A palliative, nonoperative approach should be offered for patients with poor performance status, multiple sites of obstruction, carcinomatosis, or ascites. Recurrent obstruction may be as high as 50% in these patients. Patients not suitable for surgical intervention or who refuse surgical care, should receive pharmacological therapy with the aim to reduce bowel edema and inflammation and improve symptoms such as pain, nausea, and vomiting. Combination of medications including antiemetics, drugs to reduce gastrointestinal secretions, anticholinergic medications to reduce peristalsis and secretions, opioids for pain control, and corticosteroids to decrease the tumor-associated edema (and act as antiemetics) are also widely utilized. Patients who are not operative candidates and do not respond to medical management may still benefit from endoscopic stenting or gastrostomy tube placement. The goals of medical management should be aimed at limiting pain and improving quality of life. In cases of overwhelming cancer burden or transition to comfort care, artificial nutrition and hydration may be discontinued. The focus of care should be shifted to symptom relief and hospice care.

Clinical Presentation and Initial Assessment

Patients often initially present with nausea, emesis, and abdominal pain. Depending on the location of the obstruction as well as whether the obstruction is partial or complete, patients may or may not initially present with abdominal bloating and distention. A patient with a proximal obstruction or tumor encasing the proximal small bowel may not present with distention, but rather severe nausea and emesis, often projectile in nature.

Clinical evaluation of SBO should begin with identifying the where, when and how of the patient symptoms—where the obstruction is (proximal or mid-small bowel versus large bowel), when symptoms started and their duration, and how complete (or partial) obstruction appears to be. A clinical estimate of the level of obstruction may be made from the frequency of the pain (short intervals tend to correlate with SBO versus longer intervals typical of large bowel obstruction) and distention. The duration of symptoms should include any gradual or sudden changes in bowel habits, flatus, or bowel movements. Complete vs. partial obstruction may be inferred from current bowel activity.

Pain from SBO tends to be periumbilical and colicky initially. The colicky nature of pain is secondary to compensatory increased intestinal motility that initially occurs to counter the obstruction. However, such intestinal activity eventually subsides, and there are fewer contractions especially with the use of opioid analgesics. As hypoactivity ensues and intraluminal pressure increases, microvascular perfusion may be compromised. Obstipation may follow with complete bowel obstruction.

Differential diagnosis should include adhesive disease and hernias (including abdominal wall and internal hernias) as well as constipation, volvulus, stricture, and ileus, due to chronic narcotic use, are not uncommon scenario in cancer

patients. Additionally, neurogenic and metabolic etiologies should be entertained. History of surgeries, radiation, and any anticholinergic medications should be elicited.

A complete physical exam includes evaluation for hernias and a rectal exam to evaluate for the presence of stool in the rectal vault, obstructing rectal lesions, fecal impaction or occult bleeding. If the patient has an ileostomy or colostomy, the stoma should also be digitally examined to ensure no obstruction at the level of the fascia. Abdominal distention may lead to dyspnea. Jaundice should raise concern for involvement of the hepatobiliary tree including lymphadenopathy at the porta hepatis or liver metastases.

The most important task in the emergency department (ED) assessment is to determine whether the patient requires immediate operative intervention. Indications for immediate operative intervention include incarcerated abdominal hernia, frank peritonitis, sepsis, or other findings concerning ischemic bowel disease. Fever, tachycardia, increased fluid requirement, leukocytosis, and certainly signs of sepsis should raise concern for abscess or perforation in the setting of obstruction.

Diagnostic Workup

The diagnosis of SBO is often based on clinical findings. Predictors of small bowel obstruction are: previous history of abdominal surgery, obstipation, and abnormal distension on examination [12]. Minimum laboratory tests include blood count, lactate level, and a metabolic panel.

Abdominal X-ray should be the first imaging modality for most patients with suspected SBO coming from the emergency department due to widespread availability, easy interpretation, and low cost. A single upright chest X-ray may exclude subdiaphragmatic free air, and it is a simple and quick test to determine the need for an emergency exploration, especially in patients whose exam is unreliable (unresponsive, immunosuppressed, chronic opioid users, or elderly patients). A plain abdominal film might be used initially to localize the level of obstruction (proximal vs. distal) and also as baseline for patients' undergoing nonoperative management. It is the authors' preference to initially evaluate patients with SBO with plain abdominal films unless there is a clear indication for emergency exploration. Air-fluid levels and bowel loops in the same place on supine and upright films indicate fixed adhesions.

Computed tomography (CT) scan with IV contrast is an important tool in diagnosis and preoperative planning in stable patients without indication for emergency exploration. CT may delineate a lesion, level of obstruction, and the severity of obstruction including any transition point (Fig. 26.1) or closed loop obstruction, and other radiographic evidence of ischemia. CT should be taken with intravenous contrast while enteral contrast is not necessary. In high-grade SBO, oral contrast may delay diagnosis and cause patients discomfort and possibly even complications such as aspiration.

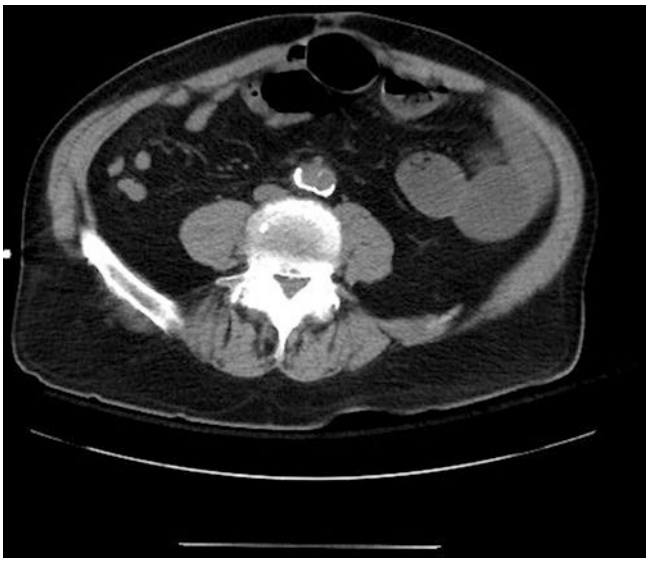

Fig. 26.1 CT—transition point in setting of complete mechanical small bowel obstruction

The most common cause of bowel obstruction is postoperative adhesions as previously mentioned. The diagnosis of adhesions is made by locating the point of obstruction (transition between dilated and decompressed bowel) without identifiable cause of obstruction, such as neoplasm, hernia, or inflammatory condition. The ability of CT scan to identify a transition zone ranges from 63–93% [12, 13].

CT imaging features in small bowel obstruction indicating the need for surgical intervention include small bowel ischemia, closed loop obstruction, and perforation. Contrast-enhanced CT has a sensitivity of 75–100% and specificity of 61–93% in the identification of ischemic SBO [12, 13]. Radiographic signs of ischemia in bowel obstruction include decreased enhancement, mucosal thumbprinting, bowel wall thickening, mesenteric edema, and pneumatosis intestinalis. Closed loop obstruction results from obstruction of a segment of bowel at two different points, and, as a consequence, this obstructed segment of small bowel is isolated from remainder of the gastrointestinal tract. CT scan might differentiate between complete and partial bowel obstruction. Complete SBO is characterized by an abrupt cutoff with air-fluid levels that suggests complete obstruction, while the presence of gas throughout the colon suggests ileus versus partial obstruction. CT is also particularly important for those patients with past medical history of cancer, to assess potential recurrence and/or progression and allow proper cancer staging in the setting of SBO.

Although CT is considered a first-line test in diagnosis, it exposes patients to radiation and it is an expensive modality. Abdominal ultrasound (US) has been investigated as a possible option for diagnosing SBO. The advantages of US include rapid diagnosis and serial assessments without radiation exposure. However, it is operator-dependent. Comprehensive and bedside US have sensitivity ranging between 83% and 97.7%, and specificities between 84% and 100% [14]. US has potential limitations such as if the presence of air limits visualization of underlying structures in the presence of dilated loops of bowel. Further testing then becomes necessary when US fails to identify the cause of the SBO. Diagnostic US findings for SBO include distended and collapsed bowel segments in close proximity, free peritoneal fluid, inspissated intestinal content, paradoxical peristalsis, highly reflective fluid within the bowel lumen, bowel wall edema between serosa and mucosa, or a fixed aperistaltic loop concerning ischemia.

Treatment and Operative Intervention

All patients should have initial management with volume resuscitation, bowel decompression, and rest with correction of metabolic abnormalities (Fig. 26.2). Unless there is indication for immediate intervention, initial pharmacologic management should be centered on antiemetics, analgesics, and antisecretory medications. Prospective trials have evaluated the use of somatostatin with decreased distention and nausea, allowing for effective nasogastric tube decompression and symptom management in poor surgical candidates [15, 16]. After the initial conservative management, different treatments options are available depending on the etiology of SBO.

Adhesive Disease Current guidelines for the management of adhesive SBO recommend that in the absence of signs of bowel ischemia, non-operative management should be tried for up to 3 days as long as the patient does not deteriorate with symptoms suggesting intestinal ischemia [17, 18]. Nonoperative management consists on bowel rest and decompression using nasogastric tube or long intestinal tube, analgesics, and antiemetics if necessary. Conservative management is effective in approximately 70–90% cases [16].

Possible adjunct to nonoperative management is the use of water-soluble contrast agent (WSCA). WSCA creates an osmotic gradient, which then increases bowel transit. A recent systematic review and meta-analysis [19] has shown that WSCA has a sensitivity of 92% and a specificity of 93% in predicting resolution of bowel surgery and that diagnostic accuracy increased significantly if abdominal X-ray is taken after 8 h from the administration. The administration of WSCA reduces the need for surgery (OR 0.55, $p = 0.003$), length of stay (−2.18 days, $p < 0.00001$), and time to resolution (−28.25 h, $p < 0.00001$), without adding morbidity and mortality.

If conservative approach fails after 3 days and/or patients deteriorates, the next step is surgical management, which includes adhesiolysis and small bowel resection if necessary. Although laparoscopic approach might be considered as first option, especially in patients with previous minimally invasive approach, the feasibility of a laparoscopic procedure in the setting of an abdomen with distended loops of bowel and potential complex adhesions could increase the risk for patients' complications. Some authors have reported an increased risk of bowel injury and need for bowel resection in laparoscopic adhesiolysis compared to open approach (53.3% lap vs. 43.3% open). Predictors for a successful laparoscopic adhesiolysis are the following: ≤2 previous laparotomies, appendectomy as past operation, no previous median laparotomy and single adhesive band [20]. Laparoscopic approach should be carefully evaluated in patients with previous oncologic abdominal procedure, where extensive procedure might have created adhesions too extensive to be treated with a minimally invasive approach.

Small Bowel Intussusception In patients with a small bowel intussusception indications to proceed immediately to the operating room include clinical or radiographic evidence of bowel compromise and peritonitis. In patients with no prior history of operation, cancer should be suspected and a low threshold for prompt surgical exploration is indicated. It is a rare cause of SBO in adults (1–5%) but is secondary to a malignant disease in up to 50% of patients [21] (Figs. 26.3 and 26.4). Strangulation is associated with high mortality rates and conventional signs of vascular compromise may not always be present [22]. Bowel telescoping will then lead to venous and lymphatic congestion, edema, and potentially ischemia and perforation.

Intussusception in the adult necessitates surgical intervention with resection of the involved bowel segment and identification of lead point after thorough evaluation of bowel and peritoneal cavity. Based on fact that half of adult patients with intussusception were noted to have a malignant neoplasm [21], appropriate oncologic workup should be completed.

Intraoperatively, bowel viability may be determined by observation of peristalsis and color, Doppler ultrasound, and occasionally IV fluorescein and Wood lamp. Tumor debulking or even an oncologic resection may be indicated. Operative decision will include whether or not to restore bowel continuity, fashion a stoma, or leave the operating room and come back for a second look laparotomy in the unstable patient. If the lesion is felt to be a primary and resectable neoplasm in a stable patient, the tumor should be resected with a wide margin proximal and distal to the lesion of normal bowel including the lymph node basin for the involved segment.

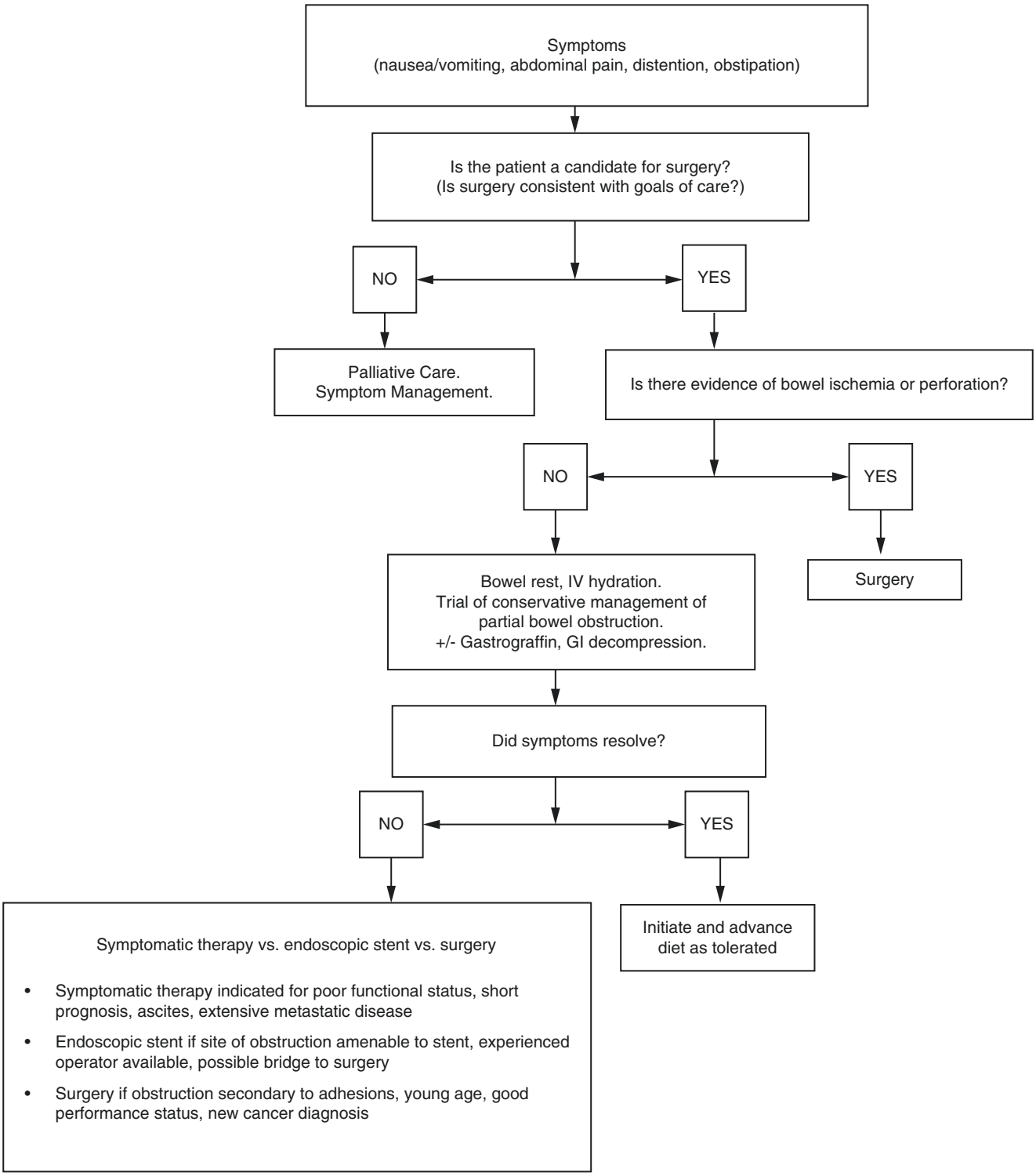

Fig. 26.2 Small bowel instruction intervention algorithm

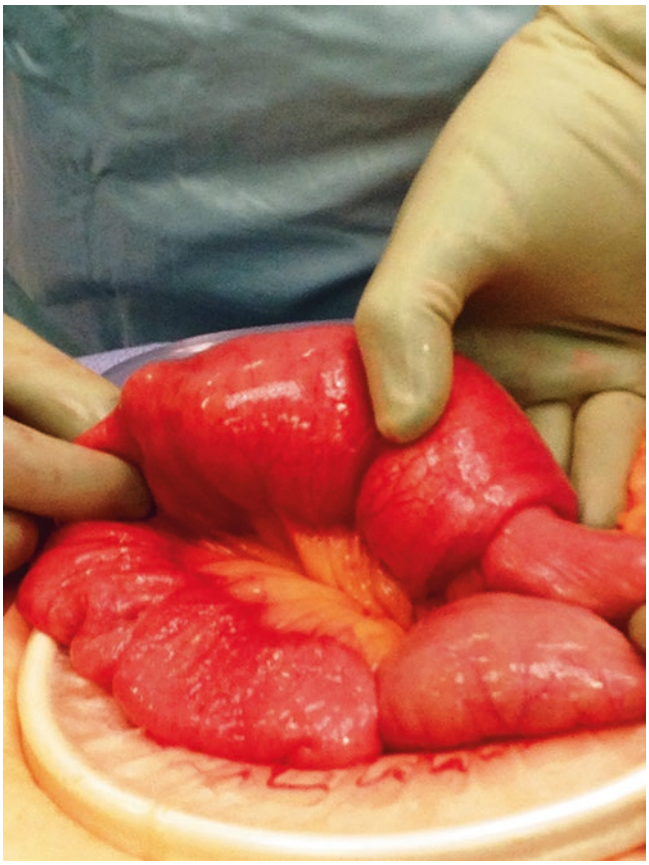

Fig. 26.3 Intraoperative intussusception with bowel telescoping

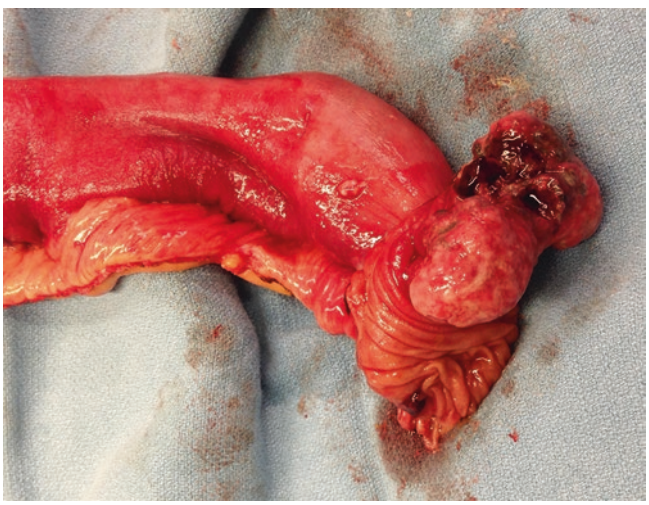

Fig. 26.4 Intraoperative intussusception with malignant lead point

Malignant Small Bowel Obstruction (MaSBO) MaSBO is usually caused by locally advanced or metastatic cancer and management is still controversial. Song et al. [9] looked at patients with MasBO from the National Surgical Quality Improvement Program between 2005 and 2017 and compared them to patients with SBO from nonmalignant causes. Of 46,706 patients studied, 1612 (3.5%) had MaSBO. The oncologic patients were more likely to have recent weight loss (22% vs. 4.0%, $p < 0.001$), severe hypoalbuminemia (18.6% vs. 5.2%, $p < 0.001$) and pancytopenia (with anemia defined as hematocrit <30%, thrombocytopenia defined as $<150 \times 10^9$ cells/L and white blood cell count $<4 \times 109$ cells/L). The risk of mortality for the oncologic patients was higher (OR 3.3, $p < 0.001$). Factors associated with 30-day postoperative mortality are advanced age (over 70), wound status, impaired functional status, low body mass index, low album level (<2.5 g/dL) as a surrogate of nutritional status, smoking history, thrombocytopenia ($<150 \times 10^9$ cells/L) and elevated WBC count ($\geq 11 \times 10^9$ cells).

Considering the high morbidity and mortality, small bowel obstruction in the setting of suspected or known malignancy should include consideration and discussion of goals of care and quality of life in view of life expectancy and overall disease burden. Efforts should be made early in the hospital course to work collaboratively for a treatment plan incorporating patient and family values with a clear discussion regarding the limitations of surgery. A comprehensive and multidisciplinary treatment plan should include consultation with medical oncologists, palliative care specialists, gastroenterologists, radiologists, and dieticians. Considering all factors, up to 50% of patients with MaSBO are deemed inoperable [10]. Surgery might increase overall survival, but morbidity (7–44%), mortality (6–32%), readmission (38–74%) and recurrent obstruction (6–47%) are frequent [23]. In case of surgery, bowel resection when feasible provides the best outcome. Otherwise, bypass should also be considered as well as fecal diversion and gastrostomy tubes for decompression [10].

A palliative, nonoperative approach should be offered for patients with poor performance status, multiple sites of obstruction, carcinomatosis, or ascites. Further details about palliative management of malignant small bowel obstruction can be found in the chapter dedicated to palliative treatment.

Large Bowel Obstruction Large bowel obstruction (LBO), while less common overall than SBO, is more likely to be secondary to malignancy. While SBO can be managed conservatively in approximately 70% cases, LBO requires surgical intervention in 70% of cases. In Western countries, colorectal cancer represents the most common cause of mechanical obstruction and is responsible for 50% of LBO. LBO occurs at initial presentation in 10% of patients with colorectal cancer [24]. The second most common cause for LBO is diverticular strictures accounting for 10–20% of cases. Colonic volvulus, generally cecal or sigmoid, is the third most common cause and it is responsible for 10–17% of cases. Among sites for colonic obstruction, the sigmoid colon is the most common followed by descending colon, splenic flexure, transverse colon, rectum, and ascending colon.

Clinical Presentation and Initial Assessment

Patients with LBO may present similarly to patients with SBO with abdominal distention, absence of flatus and/or bowel movements, and crampy abdominal pain. Physical examination should again pay special attention to evidence of dehydration and hypovolemia as well as hernias with a rectal exam performed to evaluate for the presence of stool in the vault, an obstructing rectal mass or bleeding.

Diagnostic Evaluation

Large bowel obstruction should be worked up similar to SBO. Plain abdominal X-ray has 84% sensitivity and 72% specificity and might be able to reveal the degree of bowel distension and sometimes it is able to localize the presence of transition point. CT abdomen-pelvis with venous contrast is the modality of choice to evaluate the extent and level of obstruction (Fig. 26.5). CT is estimated to have 95% sensitivity and 93% specificity for the diagnosis of LBO.

Treatment and Operative Intervention

All patients should be placed on bowel rest with fluid resuscitation. If the ileocecal valve is incompetent and there is also small bowel distention, nasogastric decompression may be indicated. Partial colonic obstruction should be attempted to be treated conservatively with the hope that a patient can undergo a single-staged planned oncologic resection in an elective situation.

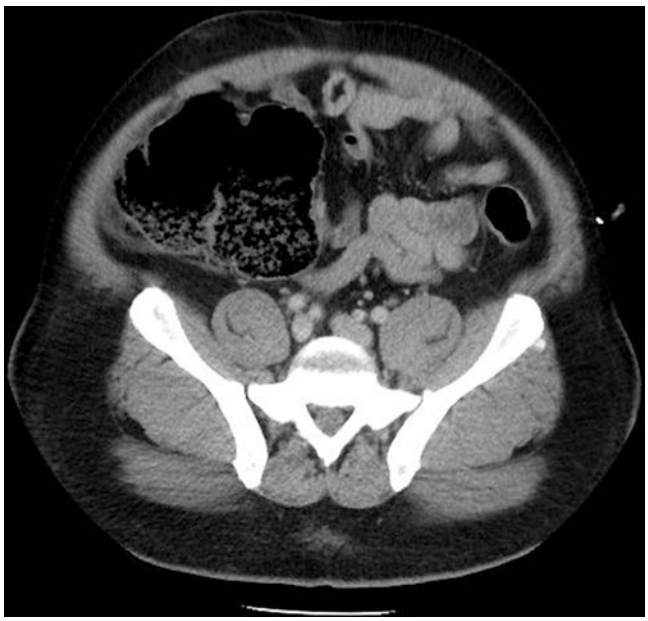

Fig. 26.5 CT—right colon/cecal dilatation in setting of partial large bowel obstruction

For primary right- sided obstructive colon cancer, general consensus is for primary resection with ileocolonic anastomosis [25, 26]. For unresectable right-sided colon cancer, a side-to-side anastomosis between terminal ileum and transverse colon as an internal bypass can be performed. Alternatively, in the presence of small bowel distension, a loop ileostomy for palliation should be considered. Optimal management of left-sided malignant bowel obstruction is controversial and it is dictated by patient and disease-related factors and available resources and technical skills. Recommendation and guidelines in the literature are at best conflicting [27]. Different surgical options have been explored for left-sided malignant bowel obstruction including primary resection, with or without anastomosis, subtotal colectomy, with or without anastomosis, or diverting stoma. Emergency surgery is associated with mortality rates three times higher than elective resection [28]. Primary resection with/without anastomosis is the most frequent recommended procedure [27]. A Hartmann's resection is an option when the anastomosis is associated with prohibitive risks.

An additional option to bridge to definitive surgery is the use of self-expanding metallic stents (Fig. 26.6) and therefore a gastroenterology consultation may be indicated in the ED. Stent placement can be followed by elective colonic resection (Fig. 26.7) after medical optimization, bowel preparation cancer staging [29, 30]. Self-expanding colonic stents as a bridge to surgery have resulted in high rates of primary anastomosis, less permanent stomas, and lower wound infection rates, without increasing the rate of mortality compared to emergency surgery. In one study, nearly three quarters of patients in the stented left-sided large bowel obstruction group underwent successful one-stage operation versus closer to one quarter with emergency surgery. Initial technical success rates have been quoted as high as 90% with prompt colonic decompression and overall 30-day mortality of less than 2% [31]. Another important advantage of stenting is that it allows a complete cancer staging and discussion at the multidisciplinary meeting, with consensus about the most appropriate treatment and a definitive procedure performed by the appropriate surgeon. Despite all these theoretical advantages, a recently published phase III randomized controlled trial comparing stenting as a bridge to surgery with emergency surgery for left-sided malignant bowel obstruction did not show a difference in mortality at 1 year [32].

Palliative Treatment At present, majority of guidelines recommend stenting as treatment of choice in case of need for palliative management of left-sided malignant bowel obstruction. In the palliative setting, colonic stenting results in faster resumption of oral intake and shorter hospital stay.

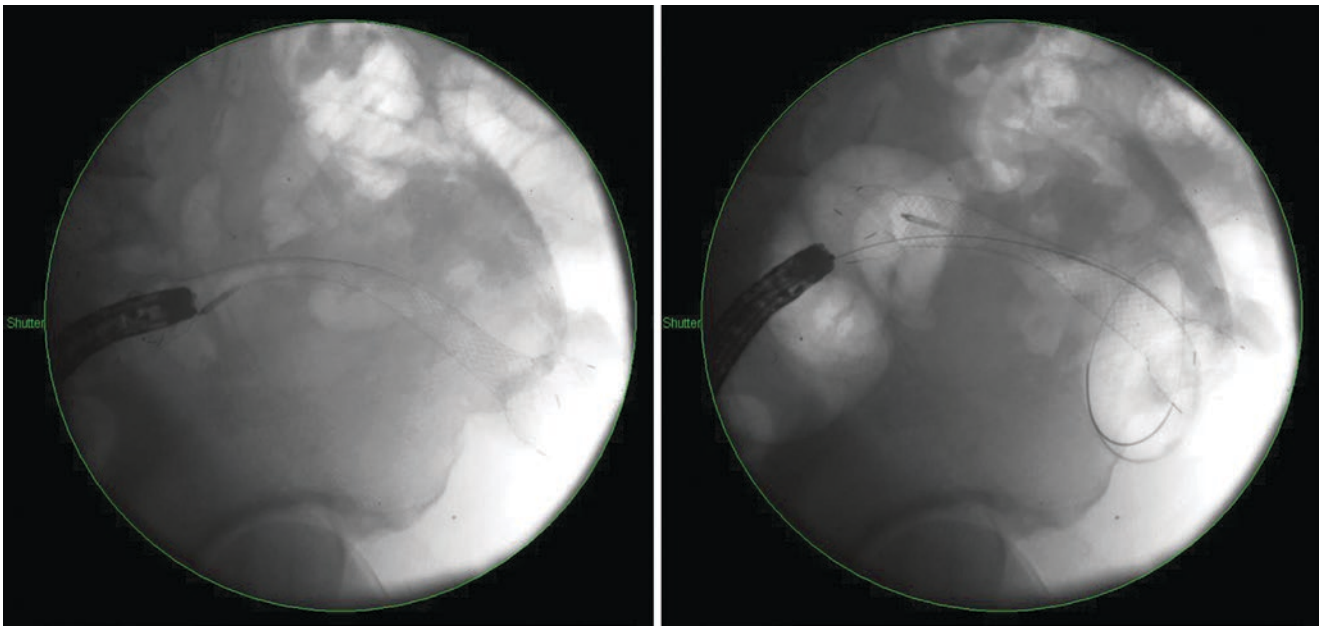

Fig. 26.6 CT—stent deployed in malignant bowel obstruction

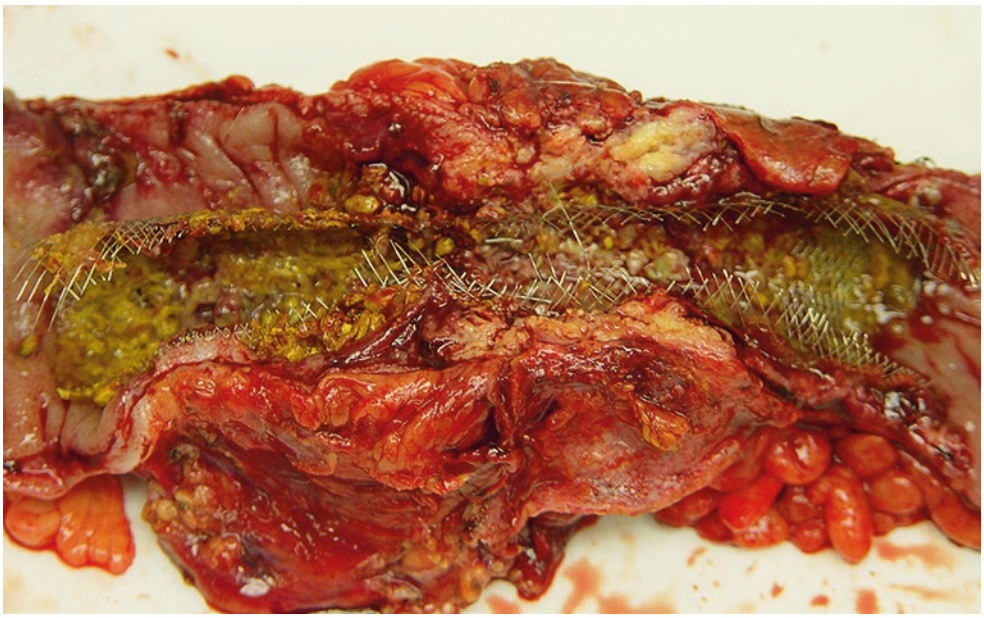

Fig. 26.7 Large bowel specimen with stent in place

Complication rates are relatively low and include stent migration, perforation, and re-obstruction [27, 31].

Main reason to prefer stent is that as previously mentioned, emergent colonic surgery is associated with a significantly higher morbidity and mortality than elective surgery. The bowel is often friable and distended with significant stool burden, and the patients are often malnourished. Postoperative complications, re-obstruction rates, and readmission rates are high for palliative malignant bowel obstruction surgery [27]. Should the decision be made to proceed with operative intervention without colonic stenting, patients should be selected based on favorable prognostic features.

Gastric Outlet Obstruction

Advanced malignant disease in the upper gastrointestinal tract might result in gastric outlet obstruction (GOO). The most common malignancies that result in GOO are pancreatic cancer, which accounts for 15–20% cases, periampullary cancer, advanced gastric cancer, duodenal/jejunal cancer, and lymphoma. Less commonly, GOO is seen in cases of gallstone impaction, gastric polyp prolapse, PEG tube migration, or gastric volvulus.

Clinical Presentation and Initial Assessment

Patients will present with progressive symptoms, predominantly nausea and vomiting, often projectile, weight loss, abdominal discomfort, cachexia, poor nutritional status, and severe dehydration. Early symptoms may include early satiety and bloating. Patients with malignant disease may have a fairly short duration of symptoms, and symptoms may be intermittent until obstruction is complete.

Median survival in the palliative setting is usually only 7–20 weeks, and for this reason, it is important to reestablish oral intake quickly to improve quality of life.

Diagnostic Evaluation

Initial evaluation should begin with an abdominal X-ray film. Patients with gastric outlet obstruction will have a gastric bubble if no nasogastric tube has been placed, with little or no air in the small bowel or the colon on radiographic imaging. CT imaging offers the advantage of identifying the obstruction and underlying lesion(s).

Barium swallow is a dynamic study and may distinguish GOO from delayed gastric emptying, anastomotic leak, or gastric fistula in the postoperative setting. Evaluation will generally proceed to EGD for both diagnosis and potential treatment with balloon dilation or self-expanding metallic stenting to improve gastric emptying. Differential diagnosis should include gastric dysmotility as well as dysphagia secondary to chemoradiation and anastomotic leak or gastric fistula in the postoperative setting.

Treatment and Operative Intervention

Therapy for GOO should begin with nasogastric decompression and fluid resuscitation and correction of the metabolic sequelae are often seen. Surgical and GI consultation should be sought for treatment planning.

Surgical gastrojejunostomy, often with a concomitant biliary bypass, is currently performed by a laparoscopic or open approach. Patients who are not considered surgical candidates are referred for endoscopic stent placement. For this reason, majority of the studies that have compared surgical jejunostomy and endoscopic stenting have been biased based on patients' selection. Self-expanding stent is inserted under combined endoscopic and fluoroscopic guidance to restore the patency of the stomach and/or duodenum and allows patients to receive nutrition and hydration via the oral route. Stents have the advantages of a short hospital stay compared to palliative surgery but they are also associated with complications such as bleeding, migration, obstruction, and fractures [33]. Palliative resection results in better long-term outcomes in appropriate candidates. Stenting it is also recommended in patients with GOO secondary to newly diagnosed gastric cancer as a temporizing measure prior to complete oncologic workup and treatment. In patients with GOO secondary to lymphoma, chemotherapy is the first-line indicated therapy. Symptom recurrence with duodenal stents is seen in the majority of patients who survive longer than 6–12 months, and the stent often needs to be replaced.

EUS-guided gastroenterostomy consists on placing a lumen-apposing metal stent under endoscopic ultrasound guidance. According to a recent meta-analysis, EUS-guided gastroenterostomy is an effective and safe minimally invasive treatment for benign and malignant GOO [34]. In contrast with endoluminal stents, EUS-guided gastroenterostomy involves placement of a fully covered stent during a bypass, and the stent is placed away from the tumor, without the risk of tumor ingrowth and occlusion.

Gastrointestinal Bleeding

Acute gastrointestinal bleed (GIB) (Fig. 26.8) may present in the patient with an established cancer diagnosis in a variety of clinical settings. Also, GIB can be the first symptom which allows the diagnoses of cancer such as colorectal cancer.

Bleeding can also be exacerbated or caused by medications such as bevacizumab, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticoagulants, commonly used medications in cancer patients. Anti-inflammatories are often used to treat pain for patients with advanced cancer, but their antiplatelet and anticoagulant properties should be considered. Moreover, patients with advanced cancer are often on anticoagulants such as warfarin or enoxaparin, and the considerations of the risks of further bleeding against the risks of deep venous or pulmonary thromboembolism should be considered. Among patients on anticoagulation, patients with cancer develop bleeding complications at a higher rate than those without cancer.

The effect of chemotherapy agents and radiation therapy on thrombocytopenia should also be considered, as this may increase the risk of bleeding. If considered a critical contributor, these agents may be held to allow bone marrow recovery and resolution of thrombocytopenia.

Bleeding is categorized as upper gastrointestinal bleeding (UGIB) proximal to the ligament of Treitz [35, 36] versus lower gastrointestinal bleeding (LGIB) [37]. UGIB is associated with significant morbidity and differential includes neoplasms including GISTs, esophageal and gastric varices, Mallory-Weiss tears, acute hemorrhagic gastritis and gastric/duodenal ulcers. Diagnostic differential for LGIB includes diverticular disease, neoplasms, radiation proctitis, inflammatory bowel disease (IBD), ischemia, infectious colitis, anorectal disease, coagulopathy, and arteriovenous malformations.

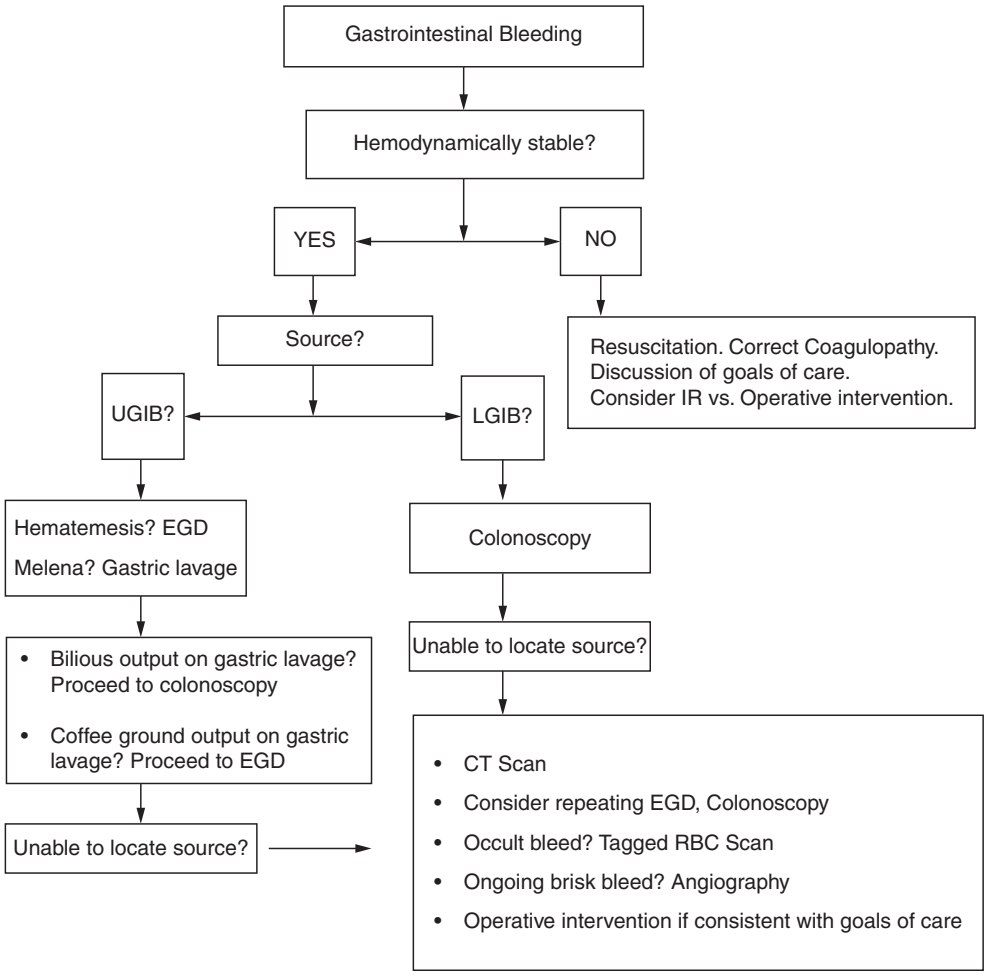

Fig. 26.8 Assessment and management of gastrointestinal bleeding algorithm

Clinical Presentation and Initial Assessment

Patients with acute UGIB may present with melena or hematemesis. Patients may endorse symptoms of hypovolemia including dizziness, dyspnea, or chest pain. Hematochezia might occur as well in patients with coagulation disorders. A history of prior episodes of bleeding is significant as 60% of patients may bleed again from the same source. Special attention should be paid to use of medications that may interfere with coagulation or alter hemodynamic response like beta-blockers. Malignancy should be suspected in a patient with a history of smoking, alcohol abuse, or *H. pylori* infection. Physical exam should begin with vital signs and an evaluation of hypovolemia. Evidence of jaundice, caput medusae, or ascites may point to hepatic disease.

Patient with acute LGIB presents usually with hematochezia, which can be mixed with clots as well. A history of previous episodes of rectal bleeding is common, or recent proctological interventions such as hemorrhoidectomy. LGIB might be present also in patients with previous pelvic malignancies treated with radiotherapy or radiochemotherapy. Radiation might cause radiation proctitis, which can be distinguished in two forms, the acute and chronic. Acute radiation proctitis occurs within 3 months of radiation therapy in 13% of patients, it is usually self-limiting and characterized by diarrhea, urgency, tenesmus, and rectal bleeding. Chronic radiation proctitis occurs in 5–10% of patients after 3 months of therapy completion and the typical complaint is rectal bleeding, while less frequent might cause rectal stenosis. Ulcerative or Crohn's colitis can present with bleeding and are a risk factor for the development of colorectal cancer. In case of rectal bleeding, a complete abdominal exam including rectal exam with proctoscopy should be performed. Even in this case, attention should be paid to current patient's medications.

Diagnostic Evaluation

Initial ED evaluation should include physiological parameters, such as heart rate, blood pressure, respiratory rate, oxygen saturation, and mental status. Initial management should

ensure adequate IV access, either large-bore peripheral IV lines or a central line as indicated. Resuscitation is essential and coagulopathies should be corrected. Urinary output and mental status, markers of end-organ perfusion, should be monitored. Early GI consultation is recommended.

A nasogastric tube is often placed for gastric lavage. A positive aspirate of gross blood or coffee-ground appearance, indicated UGIB should be followed by esophagogastroduodenoscopy (EGD). A bilious aspirate should be followed by colonoscopy. Blood tests should include hemoglobin level, hematocrit, platelet count, prothrombin time, INR, BUN, creatinine, electrolytes, liver function tests, and blood cross-matching.

Treatment and Operative Intervention

PPI therapy should be initiated at the suspicion for UGIB. Crystalloids are recommended for volume replacement.

Coagulopathies should be corrected in these cases. Severe thrombocytopenia may lead to spontaneous GI hemorrhage. The American Society of Clinical Oncologic recommends a prophylactic platelet threshold for transfusion: 10,000/μL for adult patients with leukemia, and multiple studies have found decreased frequency and severity in gastrointestinal hemorrhage in patients with platelet counts above 20,000/μL versus 10,000/μL or 5000/μL [38].

EGD and colonoscopy may be both therapeutic and diagnostic. Erythromycin can be given prior to endoscopy to facilitate gastric emptying, decreasing the need for multiple endoscopic evaluations. Therapeutic endoscopic maneuvers include injection of vasoconstrictors or sclerotherapy, thermal coagulation, and mechanical occlusion of bleeding sites (including clips, bear claw, and over-the-scope clips application). In cancer patients with cirrhotic liver disease, rubber banding, sclerotherapy, or temporizing balloon tamponade may control hemorrhage.

Early endoscopy (<8–12 h from presentation) is ideal in a stable patient and will offer the best chance of localizing and identifying the source of GI bleed and intervening. Therapeutic intervention has been demonstrated to be most successful when performed within 12 h, with declining results as time passed. If bleeding recurs despite medical and endoscopic therapy, endoscopic intervention should be repeated.

Other options for localizing GIB include CT angiography (CTA) which may provide helpful information, including hyperdensity of the mesenteric fat, contrast enhancement of the bowel wall, vascular extravasation of contrast, thickening of the bowel wall, polyps, tumors, and vascular ectasia. CTA has been noted to detect arterial bleeding at rates as low as 0.5 mL/min.

Mesenteric angiography (for bleeding of at least 1 mL/min) may be useful for poor operative candidates where other measures have failed. Should embolization also fail during mesenteric angiography, and operative intervention ultimately required, the area may be still be identified for operative intervention with methylene blue infusion. A recent meta-analysis evaluating embolization therapy versus surgery for non-variceal UGIB found a lower complication rate for embolization (31% vs. 50%) but a higher rate of rebleeding (35% vs. 18%) [39]. Arteriography may be therapeutic but requires active bleeding of more than 1 mL/min and should be reserved for patients with massive, ongoing bleeding in whom endoscopy is not feasible or colonoscopy fails to reveal the source of the hemorrhage.

Colitis may also be a special consideration in the patient undergoing radiation or chemotherapy. Radiation enteritis may lead to LGIB with a minority of patients even requiring hospitalization. Most patients with colonic ischemia respond to bowel rest, IV fluids, and antibiotics.

Rectal bleeding in patients with radiation proctitis might require endoscopic and/or surgical treatment when conservative measures have failed [40]. The aim of endoscopy is to obliterate telangiectasias using different methods, such as laser and argon plasma coagulation, radiofrequency ablation, or cryotherapy. Endoscopy is successful in up to 90% of patients and it is considered the most effective treatment for bleeding associated with radiation proctitis. Surgery is the last resort and can include fecal diversion via colostomy or ileostomy to rescue bleeding and improve other associated symptoms such as tenesmus, incontinence, and pain. More aggressive procedures like proctectomy have a high complications rate (morbidity 15–80% and mortality 3–9%) and they are rarely performed [40].

Indications for emergent operative intervention include hemodynamic instability despite maximal support measures, substantial bleeding (six units or more), or bleeding that is not controlled endoscopically. Rarely, operative intervention is required. Surgical options for LGIB include segmental colectomy when the source of bleeding can be localized. If no source is found, but bleeding is clinically significant and ongoing, a subtotal colectomy should be performed with an end ileostomy and rectal pouch leaving the patient in discontinuity. Such a situation is associated with high morbidity and mortality in the unstable patient.

Neutropenic Enterocolitis

Patients with cancer often develop neutropenia secondary to chemotherapy treatment. Neutropenia is defined as an absolute neutrophilic count (ANC) <1000/mm^3. In patients with hematologic malignancies, neutropenia is commonly due to

failure of bone marrow and therapies damaging the marrow, while in patients with solid tumors, chemotherapy may lead to underproduction of hematopoietic cell lines. Neutropenic patients often have mucositis resulting in reduced enteric mucosal barrier function allowing for bacterial translocation culminating in a characteristic pathology entity known as neutropenic enterocolitis (NEC) or typhlitis.

According to a recent retrospective review [41] conducted over 8 years at MD Anderson Cancer Center among 49,244 patients with neutropenia, 2.7% of them developed NEC, of those 94 (70%) had hematologic malignancies and 48 (36%) underwent hematopoietic stem cell transplantation. Neutropenic enterocolitis can be fatal, resulting in sepsis (11%), focal bowel ischemia and necrosis (2%) and perforation (2%) in patients who are severely immunosuppressed. The cecum is the most commonly affected site likely secondary to its vascularization and distensibility. NEC is associated with severe morbidity and mortality between 74% and 97% [41, 42]. Factors associated with worse prognosis are age, severe neutropenia (<500 cells/μL), prolonged neutropenia, and concomitant systemic infection.

Clinical Presentation and Initial Assessment

The classic presentation of neutropenic enterocolitis is a patient with absolute neutrophil count <1000 cells/μL, new onset abdominal pain and fever. Most commonly, it occurs 2–3 weeks after receiving cytotoxic chemotherapy, when neutropenia is most profound. Patients may have nausea, vomiting, diarrhea, and hematochezia. Patients with prior episodes of neutropenic enterocolitis are at risk for recurrent episodes.

Differential diagnosis should include graft-versus-host disease after allogeneic hematopoietic cell transplantation, infectious colitis including *Cytomegalovirus* and *C. difficile* colitis and *Norovirus* in immunocompromised hosts, ischemic colitis (more commonly left-sided), appendicitis and colonic pseudoobstruction.

Diagnostic Workup

Evaluation should begin with full infectious workup including blood and stool cultures and *C. difficile* toxin assays. Endoscopic findings include ulcerative inflammation, which is present in 50% of cases, nonulcerative inflammation and active bleeding in 40% of cases; colonoscopy is relatively contraindicated and may cause cecal perforation. CT findings may include bowel wall thickening, mesenteric stranding, bowel dilatation, mucosal enhancement, and pneumatosis (Fig. 26.9).

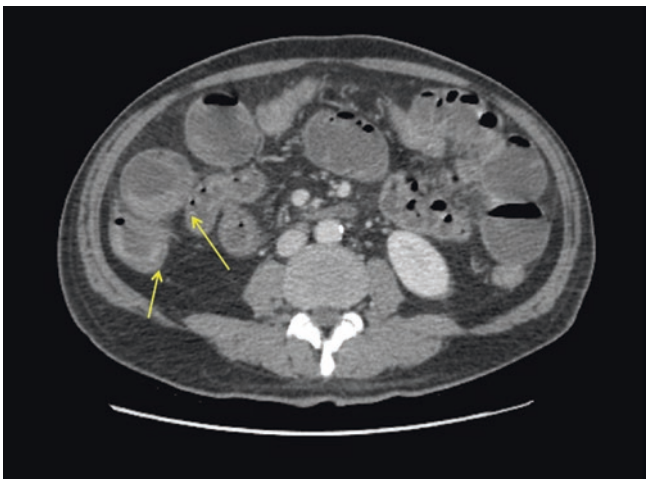

Fig. 26.9 CT—small bowel dilation with diffuse wall thickening and mucosal enhancement in setting of neutropenic enterocolitis

Treatment and Operative Intervention

First-line treatment is conservative, with nasogastric decompression when significant small bowel dilatation is present, intravenous fluids, nutrition support, broad-spectrum antibiotics and blood product support as needed. Broad-spectrum antibiotic regimen should include agents that are active against *Pseudomonas aeruginosa*, *Escherichia coli*, other enteric Gram-negative bacilli and anaerobes. Coverage for *C. difficile* should be included until ruled out. Antifungal coverage should be considered. Antidiarrheal and narcotic pain medications should be avoided. Sepsis is the most common cause for mortality in this group of patients.

Surgical intervention is indicated for patients with bowel ischemia, free perforation, peritonitis, and severe hemorrhage despite correction of coagulopathies. The most common operation performed is right hemicolectomy with formation of stoma, while extended colectomy is rarely indicated and should be avoided.

Radiation Enteritis

Radiation enteritis is an inflammatory process within the intestinal mucosa as a consequence of radiation exposure and might affect both small and large bowel injury due to radiotherapy leading to inflammation, edema, and decreased bowel function. Radiation enteritis and radiation proctitis may be classified as acute versus chronic and localized versus diffuse. Despite attempts to protect the bowel from the radiation field when possible, gastrointestinal epithelium is especially susceptible to injury given its high proliferative rate. Cell damage in the mucosa leads to microvascular damage, inflammation, edema, and decreased absorptive capac-

ity. Initial damage may be seen in hours and continue for weeks. Damage to the intestinal mucosa may lead to fibrosis, perforation, fistulae, or abscess.

There is a lack of consensus about diagnostic criteria and often symptoms are underreported by patients; as a consequence, only a minority of them are reviewed by gastroenterologists. Despite lack of diagnosis, 90% of patients have gastrointestinal symptoms in the first few weeks after receiving abdomino-pelvic radiotherapy and almost 90% of patients report chronic changes in their bowel habit with important consequences in quality of life due to these symptoms. Acute radiation enteritis may occur even transiently in up to 75% of patients undergoing radiation therapy for abdominal and pelvic cancers. Chronic radiation enteritis may occur in closer to 5–20% of patients.

Risk factors might be divided in treatment-related, including radiation dose and fractionation schedule, treatment field size, and intestinal volume irradiated, which is the main determinant of intestinal radiation-induced toxicity. Other patient-related risk factors are: diminished splanchnic perfusion secondary to diabetes mellitus or atherosclerotic disease, hypertension, tobacco smoking, BMI lower than 30, and advanced age. Concomitant administration of chemotherapy is another factor due to increased toxicity for cumulative effect. Previous abdominal surgery is an increased risk of radiation enteritis due to fixed bowel position due to postoperative adhesions.

Clinical Presentation and Initial Assessment

Acute radiation enteritis usually occurs in the second week post-radiotherapy, with a peak on week 4–5. Clinical manifestations include nausea, vomiting, abdominal pain, diarrhea associated with blood and mucus, hematochezia, tenesmus, and incontinence. A possible consequence is systemic sepsis due to bacterial translocation through inflamed intestinal mucosa. Given the diminished absorption compounding an often preexisting cancer-related anorexia, patients often are dealing with malnutrition and weight loss. Patients may bleed from ulceration, have signs of systemic infection from abscess, or present with obstructive symptoms.

Chronic enteritis might occur between 2 months and several years after radiation treatment. Symptoms include chronic abdominal pain, malabsorption, and weight loss, diarrhea, GI bleeding and complications secondary to strictures and fistulae such as obstruction and perforation. Differential diagnosis for the chronic form includes tumor recurrence, inflammatory bowel disease (ulcerative colitis, Crohn's disease), ischemic colitis, infectious colitis, STD proctitis (e.g., lymphogranuloma venereum, and gonorrhea) and inflammatory bowel syndrome.

Diagnostic Evaluation

The diagnosis of acute form of radiation enteritis is mainly clinical, with symptoms previously described, which might be only transient. If more severe a CT scan should be performed to rule out possible serious consequences, such as perforation and or obstruction.

The chronic form might be diagnosed again through patients' symptoms. Obtaining an abdominal CT/MRI is important because both sensitive at delineating subtle strictures and mucosal irregularities as well as cancer recurrence. A further endoscopy evaluation might be considered to evaluate mucosal inflammation, ulceration and possible fistulae/stricture formation, while allowing biopsies.

Treatment and Operative Intervention

Most cases of acute radiation enteritis are self-limited and should be treated with supportive therapy. Initial management includes elemental diet, IV hydration, bowel rest and ± octreotide. Diarrhea can be reduced by the use of bulking agents and antimotility drugs such as loperamide. Antispasmodics and antiemetics might be used for symptoms relief; opioids have the dual function of reducing intestinal motility and providing analgesia. Persistent symptoms despite medical interventions may require a surgical consultation.

In patients with chronic radiation enteritis, conservative management as above is employed, however, up to 30% require surgical intervention to relieve symptoms of obstruction secondary to luminal strictures and to manage fistulae, perforation and/or bleeding. As this is a high-risk intervention with postoperative morbidity and mortality rates of 30% and 5% respectively [43], patient selection is important.

Conclusion

The acute abdomen in the patient dealing with either a new or established cancer diagnosis creates a special challenge for the ED physician to individualize decisions, keeping in mind goals of care and the patient's wishes. One must maintain a broad differential diagnosis and cancer-specific considerations need to be maintained. Evaluation and intervention should proceed with the involvement of a multidisciplinary care team with the patient in the center. Caring for a cancer patient in the setting of an acute change in condition ultimately means knowing not only what is possible surgically and what is indicated medically, but also evaluating what is right for the patient overall.

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Diarrhea

27

Sai-Ching Jim Yeung

Case Study

A 36-year-old woman with stage 2 HER2-positive hormone receptor-negative breast cancer presented to the emergency department (ED) with the complaint of severe diarrhea. She had completed neoadjuvant chemotherapy and underwent a left mastectomy with left axillary lymph node dissection 10 days ago. She had mild postoperative wound erythema and had completed a 7-day course of oral clindamycin 3 days ago. She started having watery diarrhea 3 days ago. Two days ago, she was evaluated by the surgical team in the clinic. A stool sample was sent for *Clostridium difficile* toxin analysis, and she was empirically started on metronidazole 500 mg orally every 8 hours. Over the last 2 days, her diarrhea worsened, and she had abdominal cramping and 10 stools in the past 24 hours. She was feeling weak in general and nauseous. She denied having fever, chills, or vomiting.

In the ED, her vital signs demonstrated mild tachycardia and orthostatic hypotension. She had hyperactive bowel sounds, and her abdominal examination was otherwise benign. The report of the analysis of the stool sample collected 2 days ago showed the presence of *C. difficile* toxin. Her laboratory results were remarkable for a serum potassium of 3.0 mEq/L, BUN 40 mg/dL, and creatinine 1.4 mg/dL. Abdominal radiographs showed a normal nonobstructive gas pattern.

She was admitted for intravenous fluid hydration and potassium replacement. Stool samples were collected for stool culture. Metronidazole was discontinued and she was started on oral vancomycin.

Clostridium difficile diarrhea or colitis is a well-known complication of antibiotic therapy. It is also a very common problem among cancer patients. Metronidazole treatment for *C. difficile*, however, has an approximately 20% rate of lack of clinical response and an approximately 30% rate of recurrence within 3 months. Despite the suboptimal response rate, metronidazole is a popular first-line treatment because it is safe and inexpensive.

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Introduction

Diarrhea is the frequent (>3/day) passage of loose stools with urgency and it is a frequent comorbidity or adverse event associated with therapy in cancer patients. Diarrhea in cancer patients can be severe; chronic diarrhea can cause electrolyte abnormalities and malnutrition, while uncontrolled diarrhea may lead to severe dehydration and life-threatening electrolyte abnormalities. The need to avoid recurrence of serious diarrheal complications may lead to dose reduction or discontinuation of antineoplastic therapies. Cancer patients frequently present to emergency departments with acute or chronic diarrheal complications that require emergency evaluation and treatment.

Causes

Although cancer and cancer treatments (chemotherapy, radiation therapy, surgery, targeted therapy, and immunotherapy) can cause diarrhea, emergency care providers must not forget causes unrelated to cancer, e.g., lactose intolerance, food poisoning, viral gastroenteritis, side effects of noncancer drugs, inflammatory bowel disease, and irritable bowel syndrome (Table 27.1). In this chapter, we focus on causes relevant to cancer and cancer treatments.

Paraneoplastic Syndromes

Certain cancers can cause diarrhea by secreting hormones, including the following:

- Carcinoid tumors
- Zollinger-Ellison syndrome (gastrinoma)

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Table 27.1 Causes of diarrhea in cancer patients

Paraneoplastic	Carcinoid syndrome, medullary carcinoma of the thyroid, neuroendocrine pancreatic cancer (e.g., gastrinoma, VIPoma), pheochromocytoma
Surgery related	Celiac plexus block, cholecystectomy, esophagogastrectomy, gastrectomy, pancreaticoduodenectomy (Whipple procedure), intestinal resection (malabsorption due to short bowel syndrome), vagotomy
Chemotherapy	Bortezomib, capecitabine, 5-fluorouracil, oxaliplatin, carboplatin, cisplatin, cytosine arabinoside, cyclophosphamide, daunorubicin, paclitaxel, docetaxel, doxorubicin, methotrexate, irinotecan, topotecan
Targeted therapy[a]	Gefitinib (25.9–51.6% [all grades], 1–3% [grades 3–4]) Erlotinib (18%, 3%) Afatinib (95%, 14.4%) Lapatinib (64%, 10%) Trastuzumab (3.7% [grades 3–4]) Pertuzumab (3% [grades 3–4]) Imatinib (20–26%, 1%) Pazopanib (<4%, 52%) Regorafenib (34–40%; 5–8%) Cabozantinib (64%, 12%) Sunitinib (44%, 5%) Sorafenib (55.3%, 7.8%) Ziv-afilbercept (69.2%, 19%) Axitinib (11% [grades 3–4]) Vandetanib (74%, 10%) Everolimus (1% [grades 3–4]) Vemurafenib (5–6% [all grades]) Dabrafenib (1% [all grades]) Trametinib (45–50%, 4%) Selumetinib (45–50%, 4%) Crizotinib (60% [all grades]) Bortezomib (51%, 8%)
Radiation	Radiation therapy to the abdomen, pelvis, para-aortic lymph nodes, lumbar spine
Bone marrow transplantation	Conditioning chemotherapy, total body irradiation, graft-versus-host disease after allogeneic transplants
Immune checkpoint inhibitors	Ipilimumab, cemiplimab, pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab
Infection	Neutropenic colitis, typhlitis, and ileitis. *Bacillus cereus*, *Campylobacter*, *Clostridium difficile*, *Clostridium perfringens*, *Cryptosporidium*, *Cytomegalovirus* (in immunocompromised hosts), *Giardia lamblia*, *Rotavirus*, *Salmonella*, *Shigella*
Fecal impaction	Liquid stool going around impacted stool
Comorbid diseases	Diabetes mellitus, hyperthyroidism, gastroenteritis, irritable bowel syndrome, celiac disease, inflammatory bowel disease (Crohn's disease, ulcerative colitis), HIV/AIDS
Psychological factors	Stress

[a]Percentage inside parentheses indicate the incidence rate of diarrhea of all grades and severe grades (grades 3–4), respectively

- VIPomas (neuroendocrine tumors that secrete vasoactive intestinal peptide [VIP] autonomously)
- Medullary thyroid carcinoma (sporadic, familial, or as part of Sipple syndrome—multiple endocrine neoplasia type 2 [MEN 2])
- Neuroendocrine tumors as part of the Wermer syndrome—multiple endocrine neoplasia type 1 (MEN 1)

Treatment-Induced Diarrhea

Chemotherapy In addition to cancer cells, cytotoxic chemotherapy kills other fast-growing cells, including those in the intestinal lining. Certain chemotherapeutic agents can disturb the normal absorptive and secretory functions of the small bowel, resulting in treatment-related diarrhea [1]. Chemotherapeutic agents associated with severe diarrhea include fluorouracil, capecitabine, irinotecan, paclitaxel, docetaxel, vinorelbine, etc. The diarrhea caused by irinotecan may be delayed (>24 hours) and severe. Concomitant abdominal or pelvic radiotherapy and recent gastrointestinal surgery are associated with increased severity of treatment-induced diarrhea. Platinum-based therapy can cause diarrhea and colitis. The median time from starting platinum-based therapy to colitis is 66 days and the median duration is 20 days. Colonoscopic examination will show ulceration in one third of cases and nonulcerative inflammation in the colonic mucosa in another one third of cases. About half of patients with platinum drug-induced colitis will require hospitalization [2]. Taxanes also causes colitis. The median time from start of taxanes to colitis symptom is 31 days. Colonoscopy also shows inflammation, but some patients have microscopic colitis [3].

Targeted Therapy Diarrhea induced by anti-EGFR targeted therapy is secretive and due to excess chloride secretion. For small molecule tyrosine kinase inhibitors (TKIs) targeting EGFR (see Table 27.1), diarrhea of all grades occurs in up to 60% of patients [4] and as many as 10% of cases are severe. Anti-EGFR monoclonal antibodies (mAb) (cetuximab and panitumumab) also causes diarrhea of all grades in almost a quarter of patients, and about 1–2% have severe diarrhea. In non–small cell lung cancer, the combination of anti-EGFR TKI and antiangiogenic therapy results in improved antineoplastic activity; however, these combinations also increase diarrhea [5]. The receptor tyrosine kinase (KIT) is highly expressed in the interstitial cells of Cajal, which are pacemakers for intestinal motility. Some TKIs

(e.g., imatinib and sunitinib) may induce diarrhea through inhibition of KIT. Cyclin-dependent kinase (CDK) 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) cause diarrhea of all grades in about 20% of patients and about 1% are severe [6]. PI3K inhibitors cause a watery nonbloody diarrhea in over 50% of patients [7]. An early onset, less severe diarrhea may occur at a median of 1.9 months after starting PI3K inhibitors, while a more severe diarrhea occurs at a median of 7.1 months after starting treatment. The severe diarrhea is due to immune-mediated colitis [8].

Radiotherapy External beam radiotherapy (XRT) that focuses on the thoracolumbar spine, para-aortic lymph nodes, abdomen and pelvis for cervical cancer, colorectal cancer, prostate cancer, metastatic cancer, etc., as well as pelvic brachytherapy exposes part of the intestine to radiation, causing diarrhea. Diarrhea is the most common side effect of radiotherapy. The overall prevalence of irradiation-induced diarrhea may reach 35% [9]. Factors predicting the severity of XRT-induced diarrhea include total radiation dose, fractionation, the volume of bowel exposed to radiation (related to the method of radiation such as intensity-modulated and image-guided radiotherapy [IMRT] and volumetric modulated arc therapy [VMAT]), and concurrent chemotherapy. Acute diarrhea may occur at about 10 Gy and last up to 3 months after treatment. Chronic radiation enteritis can begin months or even years after treatment. Bile acid malabsorption may be responsible for some portion of radiation-induced diarrhea [10].

Surgery Surgical treatment of cancer may involve removal of sections of the gastrointestinal tract or organs with endocrine and digestive functions. These anatomic changes may limit the ability of the gastrointestinal tract to absorb certain nutrients, e.g., fat, resulting in diarrhea. Bowel resection lessens the surface area for reabsorption of water from food. Pancreatic cancer or its surgical treatment can compromise exocrine pancreatic function, leading to lack of digestion and malabsorption. Surgical changes in biliary anatomy will also compromise emulsification of fat by bile salts and consequently digestion and absorption of fatty food. Diarrhea is also part of the dumping syndrome which occurs when undigested food moves too rapidly into the small intestine. The dumping syndrome is associated with gastrectomy, gastroenterostomy, gastrojejunostomy, vagotomy, pancreaticoduodenectomy, and esophagectomy.

Bone Marrow Stem Cell Transplant In stem cell transplantation, conditioning chemotherapy and total body radiation may cause diarrhea. In autologous peripheral blood stem cell transplantation, in addition to side effects of chemotherapy and radiation, antimicrobials and infectious complications (including *C. difficile*) can also cause diarrhea. *Clostridium difficile* is the most common pathogen with an incidence of 15% during the 7 days before, and the first 30 days after, autologous transplant [11]. After allogeneic hematopoietic cell transplantation, diarrhea can be a frequent and serious complication. The diagnosis of acute graft-versus-host disease as the cause of diarrhea is straightforward if rash, jaundice, nausea, and vomiting are present [12]. However, if only diarrhea is present, the diagnosis may not be so obvious. Nevertheless, infectious (viral, bacterial, and parasitic) causes of diarrhea must be excluded before starting immune-suppressive drugs to treat graft-versus-host disease. Graft-versus-host disease-induced diarrhea usually occurs between 10 and 100 days after transplant and may resolve or become chronic.

Immune Checkpoint Therapy The most frequently seen GI complications secondary to immune checkpoint inhibitor therapy are diarrhea and colitis [13, 14]. Diarrhea can be due to immune-mediated colitis, which mainly involves the descending colon. Although immune checkpoint inhibitor-induced colitis is similar to inflammatory bowel diseases in many aspects, this immune-mediated adverse effect (irAE) can start acutely, progress rapidly, and lead to potential serious complications, including bowel perforation and death [15]. In some cases, enteritis without any colonic involvement may lead to small bowel obstruction [16].

Pancreatic toxicity associated with immune checkpoint inhibitor therapy is uncommon (<2%) and usually presents as a transient asymptomatic increase in lipase or amylase [17, 18]. Acute pancreatitis is rare [17–20] and patients present with a typical pancreatitis picture or with isolated symptoms of nausea, vomiting, fever, epigastric pain, or diarrhea [17]. Pancreatic exocrine insufficiency with or without pancreatitis manifests as irregular stools with diarrhea, discoloration of feces, and weight loss.

Infectious Enteritis Cancer patients are susceptible to infectious diarrhea. Bacteria, viruses, and parasites are all potential culprits. Neutropenia, immune suppressants, antibiotic use, and breakdown of natural defenses against microbes are all factors that increase the risk for cancer patients. *Clostridium difficile* diarrhea or colitis is a common problem.

In neutropenic patients, diarrhea, abdominal pain, and fever are symptoms of neutropenic enterocolitis. The cecum is frequently affected, often extending to the ileum, and occasionally the ascending and transverse colon.

Immunosuppression and frequent use of antibiotics in neutropenic patients alters the normal flora, leading to infection by resistant bacteria or unusual bacterial species. Bacteremia is frequent. Gram-negative rods (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella*, *Enterobacteriaceae*), gram-positive cocci (*Streptococci*, *Enterococci*), fungi (*Candida*, *Aspergillus*, or *Zygomycetes*), and viruses (cytomegalovirus) are causative organisms.

Enteral Feeding The composition of tube feeding formula may cause diarrhea. High rate of feeding and high osmolality increase diarrhea incidence. Patients selected for tube feeding are often hypoalbuminemic and data suggest that hypoalbuminemia predisposes to diarrhea by decreasing osmotic pressure and causing edema in the intestinal mucosa. Whether fiber-containing formulas can control diarrhea due to tube feeding is unclear. Contamination of feeding and food poisoning is a common problem if hand washing hygiene, clean mixing of formula, refrigerating mixed formula, and proper handling of the feeding equipment are not observed.

Celiac Plexus Block Celiac plexus block is commonly associated with a self-limiting acute diarrhea; however, occasionally, it may be persistent [21]. This diarrhea may be amenable to treatment with atropine.

Stress and Anxiety The stress and anxiety associated with cancer and treatments can cause diarrhea [22].

Medications Not Intended for Cancer Treatment Excessive doses of laxatives or magnesium-containing antacids commonly result in diarrhea.

Symptoms

Increased frequency and volume of bowel movements per day, incontinence, increase in ostomy output volume compared with baseline, the character of the fecal material (loose, very loose, watery), dizziness, abdominal pain, and fever are pieces of information needed for assessment of diarrhea severity [23]. These questions help classify diarrhea as complicated or uncomplicated and guide therapy [24]. Medication and dietary intake, as well as a history of recent travel, may provide additional etiologic clues. Weight loss and reduced urine output indicate the severity of diarrhea. Bloody stool, stool containing mucous, severe cramping, and abdominal pain are consistent with enterocolitis [25].

The National Cancer Institute Common Toxicity Criteria (version 4.03) is a frequently used standard tool for assessing diarrhea severity (Table 27.2) [26], but it does not include assessment of duration of diarrhea and stool volume. These severity parameters and other coexisting symptoms that are predictive of serious complications were addressed in the clinical practice guidelines [24, 27].

Grade 3 or 4 diarrhea is also classified as complicated. Diarrhea may be considered complicated and potentially serious if a cancer patient with Grade 1 or 2 diarrhea has the following: >6 loose bowel movements a day for >2 days, bloody stool or rectal bleeding, no urine output for >12 h, inability to drink for >1 day, weight loss due to diarrhea, diarrhea after several days of constipation, abdominal distension, or fever. In addition, moderate-to-severe cramping and nausea/vomiting, neutropenia, and the presence of systemic inflammatory response syndrome indicate potentially serious complications. Close monitoring and full investigation is warranted [24].

Diagnosis

Most chronic diarrheal paraneoplastic syndromes would have already been diagnosed in most cancer patients, and the diagnostic evaluation for the specific paraneoplastic syndromes is out of the scope of this chapter. For cancer patients presenting to EDs with diarrhea, the goal of rapid evaluation is to identify life-threatening conditions and complications requiring hospitalization. History should include medications (including antineoplastic agents), travel, and diet.

Table 27.2 National Cancer Institute grading of diarrhea

	Grade					
	0	1	2	3	4	5
Colostomy absent	None	Increase of <4 stools/day compared with baseline	Increase of 4–6 stools/day, or waking up to have bowel movements	Increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	Hemodynamic collapse or severe consequences requiring intensive care	Death
Colostomy present	None	Mild increase in loose watery output compared with baseline	Moderate increase in loose watery output compared with baseline, but not interfering with normal activity	Severe increase in loose watery output compared with baseline; or copious output that interferes with normal activity	Hemodynamic collapse or severe consequences requiring intensive care	Death

Adapted from National Institute of Health. National Cancer Institute. Common Toxicity Criteria (version 4.03) for Diarrhea
https://nciterms.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=CTCAE&ns=ctcae&code=E10575

Physical examination should assess intravascular volume status and ascertain signs of infection and abdominal tenderness.

Although a very crude estimate, information about the frequency of stools in the past 24 hours helps to assess severity of diarrhea. For immune-related diarrhea after immune checkpoint inhibitor therapy, Grade 1 (mild) diarrhea is up to four stools per day over baseline or mildly higher ostomy output from the baseline [13, 14, 16]; Grade 2 (moderate) diarrhea is four to six stools per day over baseline or moderate ostomy output; Grade 3–4 (severe or life-threatening) diarrhea is ≥ seven stools per day over baseline, with fecal incontinence. The patient may present with symptoms such as abdominal pain, rectal bleeding, and mucus in stool [14], and bowel perforation can occur [16].

Diagnostic testing and imaging studies would follow, including routine complete blood count with differential and complete metabolic panel to assess leukocytosis or neutropenia, electrolyte imbalances, liver function, and renal function. Diarrhea causes dehydration, electrolyte abnormalities, and disturbed acid-base balance. Hypokalemia and nonanion gap acidosis are the main diagnostic features of severe diarrhea. Hypokalemia necessitates aggressive potassium replacement. Prerenal azotemia or renal failure may result from severe dehydration. Other electrolytes, including calcium and magnesium, should be checked and replaced. Hypokalemia, hypomagnesemia, and hypocalcemia can cause EKG changes and cardiac arrhythmias.

Stool samples should be analyzed by culture for the presence of pathogenic bacteria, such as *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *C. difficile*, and yeast; *Clostridium difficile* testing (enzyme immunoassay for *C. difficile* toxins A and B, *C. difficile* DNA PCR); and the presence of cryptosporidium by acid-fast stains and other parasites by standard laboratory methods. In the course of cancer treatment, many patients have infectious complications and exposure to antibiotics. *Clostridium difficile*-related diarrhea should always be excluded in cancer patients who have recently been treated with antibiotics. Viral pathogens can be tested by culture (enteroviruses and adenovirus), enzyme immunoassays (rotavirus and adenovirus), or multiplex PCR. Cytomegalovirus immediate–early antigen tests of blood can detect cytomegalovirus antigenemia.

Stool analysis can classify the diarrhea as watery, fatty, or inflammatory. Watery diarrhea suggests functional, secretory, or osmotic etiology. Functional disorders such as irritable bowel syndrome and functional diarrhea are common in chronic diarrhea. Secretory diarrhea can be caused by bile acid malabsorption, paraneoplastic syndromes, microscopic colitis, endocrine disorders, and some postsurgical changes. Osmotic diarrhea can be due to laxative abuse or malabsorption of nonlipid nutrients. Fatty diarrhea reflects malabsorption of fat, which can be caused by a wide variety of causes

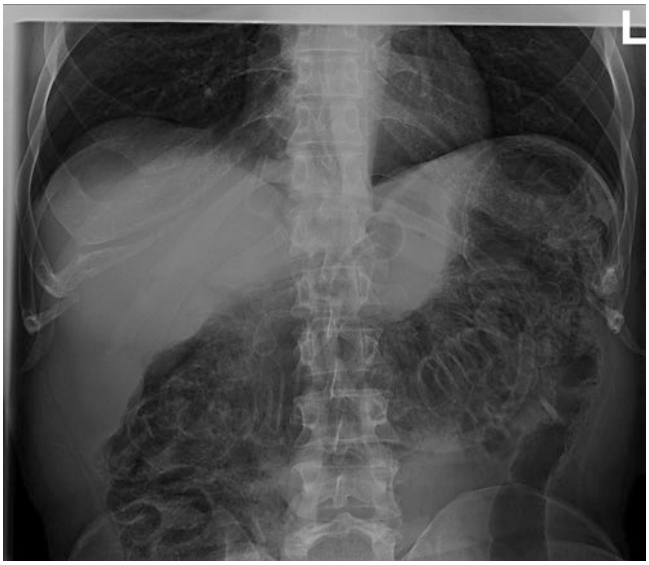

Fig. 27.1 Pneumatosis intestinalis

such as digestive enzyme deficiency, disruption of biliary function, celiac disease, or ileitis. Inflammatory diarrhea warrants further evaluation and can be caused by inflammatory bowel diseases, immune colitis, and infectious enteritis [28]. Fecal lactoferrin and fecal calprotectin can help differentiate between an infectious or inflammatory etiology and can be used to monitor disease activity and treatment response [29].

An abdominal X-ray series is helpful to quickly exclude intraabdominal free air and pneumatosis intestinalis (Fig. 27.1). The suspicion for serious gastrointestinal complication (e.g., perforation and obstruction) should be high and the threshold for CT imaging of abdomen and pelvis should be low. A triad of neutropenia, abdominal tenderness, and diarrhea should raise suspicion for neutropenic enteritis [30]. Perhaps due to neutropenia, abdominal pain or tenderness may not be prominent despite the presence of significant infection. A CT scan of abdomen and pelvis with intravenous and oral contrasts can diagnose neutropenic ileitis, typhlitis, and colitis (Fig. 27.2). MRI may be used if CT is contraindicated (e.g., if the patient is allergic to iodine contrast dyes). Bedside ultrasonic examination of bowel wall thickness can provide a rapid diagnosis [31]. Thickening of bowel wall to >4 mm for >30 mm in length is suggestive of enterocolitis [27].

In cancer patients with significant diarrhea, colonoscopic examination and biopsy are often indicated. A history of allogeneic stem cell transplantation should put graft-versus-host disease high in the differential diagnosis. Infectious colitis (e.g., cytomegalovirus colitis) is also in the differential diagnosis for immunocompromised patients. Immune colitis can also be caused by PI3K inhibitors. A history of ongoing treatment with immune checkpoint inhibition ther-

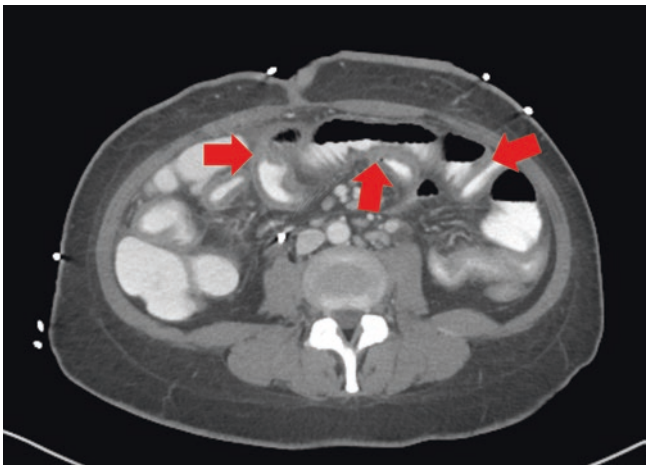

Fig. 27.2 CT scan imaging of a cancer patient with neutropenic ileitis. A neutropenic leukemic patient presents with profuse diarrhea and minimal abdominal pain but no fever. The CT scan demonstrated significant thickening of the wall of ileum (*arrows*) consistent with ileitis

apy should raise the suspicion for immune-mediated colitis, the confirmation of which would also require endoscopy, with or without biopsy. Viral colitis such as cytomegalovirus infection can also be confirmed by endoscopy with biopsies.

Management

Although many causes of diarrhea in cancer patients require specific therapies, therapies aimed at decreasing or replenishing fluid and electrolyte losses are required [32].

Diet

Regardless of the cause of diarrhea, diet modifications may decrease the symptom burden of diarrhea. Foods that may lessen the burden include the following:

- Six to eight small meals and snacks each day and increased room temperature clear liquids
- Low-fat high-potassium diet with foods containing soluble fiber
- Lactose-free
- BRAT (bananas, rice, applesauce, toast) diet

Foods that may worsen diarrhea should be avoided, such as:

- Fatty, greasy, or fried foods
- Foods high in insoluble fiber content
- Gas-forming foods
- Foods with high sugar contents
- Hot liquids
- Dairy products or foods made with significant amount of dairy products
- Foods sweetened with sugar alcohols (e.g., sorbitol, xylitol, or mannitol)
- Foods that can irritate the digestive tract (e.g., caffeine such as coffee, strong tea, sodas, tomato juice, citrus juices, and alcohol)
- Tobacco

Probiotics before or during chemotherapy may prevent chemotherapy-induced diarrhea [33]. The use of probiotics appears helpful in improving tolerance of, and support for, treatment and radiation-related diarrhea. Sources of probiotics include foods such as yogurt, buttermilk, sauerkraut, and cottage cheese. Most clinical research involves *Lactobacillus* and *Bifidobacterium* to modify gut microflora [34]. However, probiotics are not recommended in immunocompromised neutropenic patients. Food is a potential cause of invasive infectious disease in immunocompromised patients, and *Lactobacillus acidophilus* bacteremia due to yogurt ingestion has been reported in a stem cell transplant patient with mucositis [35].

Medication Adjustment

Medications such as bulk laxatives, stool softener, and promotility agents (e.g., metoclopramide) should be discontinued. Oral magnesium supplements can cause diarrhea and if significant hypomagnesemia is present, parenteral magnesium replacement may be indicated.

Correction of Dehydration and Electrolyte Imbalances

Initial treatment for severe diarrhea is aimed at correcting any volume, electrolyte, and acid-base abnormalities with IV normal saline, potassium chloride, and if acidosis is severe, sodium bicarbonate. These abnormalities are frequently severe enough to necessitate hospital admission.

Pharmacologic Therapy

Treatment goals include slowing intestinal motility, decreasing intestinal secretions, and promoting intestinal absorption. Other pharmacologic therapies for the relief of diarrhea are specific to the underlying mechanism.

- Opioids bind to μ receptors in the gastrointestinal tract and decrease bowel motility to increase transit time:

  - Loperamide; 4 mg followed by 2 mg after each unformed stool up to 12 mg/day [24, 27]
  - Diphenoxylate
  - Codeine
  - Tincture of opium
- Anticholinergics:
  - Atropine
  - Belladonna
  - Scopolamine
- Adsorbents such as kaolin, clays, and activated charcoals have been commonly used and generally considered safe:
  - Kaolin
  - Pectin
- Absorbents give bulk to the fecal material, but one potential drug interaction is that they may bind and inhibit absorption of other oral antidiarrheal medications:
  - Wheat dextrin
  - Psyllium fiber
- Somatostatin analogues:
  - Octreotide; treatment usually start with 100–150 μg every 8 hours
  - Lanreotide
  - Pasireotide
- Mucosal prostaglandin inhibitors has antisecretory effects:
  - Aspirin (may be useful for radiation-induced diarrhea)
  - Bismuth subsalicylate
- Corticosteroids reduce edema associated with obstruction and radiation colitis, reduce hormonal influences of some endocrine tumors (e.g., VIPoma), and treat immune-mediated colitis:
  - Budesonide is an oral steroid medication that is topically active in the gastrointestinal tract. It has a 90% first pass effect; therefore, after liver metabolism, the systemic availability is low
  - Dexamethasone
  - Methylprednisolone, prednisolone, or prednisone
- Antimicrobials: Quinolone antibiotics are effective for salmonellosis. Depending on the degree of immunocompromise, antibiotic treatment may need to continue for several months. Some beta-lactam antibiotics (e.g., cefotaxime, ceftriaxone) and sulfamethoxazole-trimethoprim are alternatives. Campylobacteriosis is treated with azithromycin or quinolone antibiotics, with addition of vancomycin for severe cases. Shigellosis is treated with quinolone antibiotics. Alternatives include sulfamethoxazole-trimethoprim and azithromycin. *Clostridium difficile* may be treated with metronidazole or oral vancomycin. Enterotoxigenic *E. coli* are frequently resistant to ampicillin and sulfamethoxazole-trimethoprim. Quinolone antibiotics are generally effective. Enterotoxigenic *Bacteroides fragilis* is an emerging pathogen causing diarrhea, and metronidazole has excellent activity against this pathogen
  - Bismuth subsalicylate has direct antimicrobial effects on *Escherichia coli*
  - Sulfamethoxazole and trimethoprim
  - Beta-lactam antibiotics, e.g., cefotaxime, ceftriaxone
  - Quinolone antibiotics, e.g., levofloxacin, moxifloxacin, ciprofloxacin
  - Metronidazole
  - Oral vancomycin

Management of Specific Clinical Scenarios

Treatment-Induced Diarrhea

Based on controlled clinical trials and clinical practice guidelines [24, 27], loperamide (4 mg initial dose followed by 2 mg every 4 hours) is the standard first-line therapy for chemotherapy-induced diarrhea. After loperamide for the first day of chemotherapy-induced mild diarrhea, treatment may be escalated by adding octreotide, 100–150 μg every 8 hours [23]. Severe treatment-induced diarrhea with complicated symptoms should be managed with IV fluids, octreotide acetate 100–150 μg SC three times daily or 25–50 μg/hour IV with up to a five-fold escalation as needed, and administration of antibiotics until diarrhea has stopped for >24 hours [24]. Updated guidelines stress the importance of recognizing early warning signs of complicated diarrhea and early intervention such as initiating antibiotic therapy [24].

"Complicated" Chemotherapy-Induced Diarrhea

Patients with mild-to-moderate diarrhea complicated by moderate-to-severe cramping, nausea and vomiting, diminished performance status, fever, sepsis, neutropenia, bleeding, or dehydration, as well as patients with severe diarrhea, are classified as "complicated." These patients should be evaluated further, monitored closely, and treated aggressively. Aggressive management of complicated cases usually necessitates hospital admission and involves IV fluids; octreotide at a starting dose of 100–150 μg three times daily (25–50 μg/h) if the patient is severely dehydrated, with dose escalation up to 500 μg three times daily until diarrhea is controlled, and administration of antibiotics (e.g., fluoroquinolone). These patients should be evaluated with complete blood count, electrolyte profile, and a stool work-up evaluating for blood, fecal leukocytes, *C. difficile*, *Salmonella*, *E. coli*, *Campylobacter*, and infectious colitis.

Targeted Therapy

There are no specific guidelines for the management of targeted therapy-induced diarrhea. As a secretive mechanism is the most frequent cause, the first-line treatment is loperamide and opiates, followed by octreotide.

Neutropenic Enterocolitis

The risk of mortality from neutropenic enterocolitis is high [30, 36]. In the absence of acute complications that require emergency surgery, the initial management is to use broad-spectrum antibiotics. The antibiotics chosen should cover enteric gram-negative organisms, gram-positive organisms, and anaerobes. The choice of antibiotics is basically the same as for neutropenic fever. In cases that do not respond to antibiotics, antifungal agents should be added, just as in the management of neutropenic fever. Depending on the underlying malignancy, neutropenia may not resolve quickly, even when colony-stimulating factors (filgrastim) are used.

Immune-Mediated Colitis

There are quite a few guidelines available for the management of immune-related adverse effects of immune checkpoint inhibitors, including those from the National Comprehensive Cancer Network (NCCN) [37], American Society of Clinical Oncologic (ASCO) [38], Society of Immunotherapy for Cancer (SITC) [39], and European Society of Medical Oncologic (ESMO) [40]. Management is based on grading. Grade 1: Symptomatic treatment with loperamide, oral hydration, the American Dietary Association ulcerative colitis diet, and electrolyte replacement as needed. Grade 2: Diphenoxylate/atropine may replace loperamide and budesonide (or systemically active prednisone/methylprednisolone) may be started. In grade 1 or 2 diarrhea with bleeding or persistent grade 2 diarrhea, endoscopic examination and biopsy are indicated. Grade 3 or 4: Treatment with IV corticosteroid (methylprednisolone 125 mg) and IV replacement of fluid and electrolytes should be started. Infliximab is second-line treatment and is usually started for the lack of improvement in diarrhea after treating with corticosteroids for 72 hours. Corticosteroids are typically the first-line treatment for irAE grade 2 or higher, and the primary therapy that emergency physicians will institute.

GVHD

In addition to antidiarrheal agents, glucocorticoids (e.g., budesonide), and immunosuppressive medications, the diarrhea associated with GVHD may be managed with a specialized five-phase dietary regimen [41]. Octreotide is also effective in diarrhea associated with GVHD [42, 43].

Paraneoplastic Diarrhea

Initial treatment is directed toward correcting volume and electrolyte abnormalities. Somatostatin analogues control diarrhea in up to 90% of patients. Glucocorticoids reduce symptoms in 50% of cases. Tumor resection is the treatment of choice for long-term control of symptoms. In advanced disease, tumor debulking may relieve symptoms, but it is not effective in all cases. Hepatic artery radioembolization or transcatheter chemoembolization with doxorubicin or cisplatin [44], XRT, and percutaneous or intraoperative radiofrequency tumor ablation may be attempted to reduce tumor burden.

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Constipation

28

Demis N. Lipe

Case Study

An 82-year-old male with pancreatic cancer presents to the emergency department with complaints of constipation for 5 days. He has tried over-the-counter laxatives without relief. He is nauseated, but not vomiting, and describes a sensation of pressure in his suprapubic region. He can pass gas but is having difficulty urinating. He has not had any recent medication changes. His cancer-associated pain is well controlled by his daily opioid regimen. He has a past history of constipation. On presentation, he is somewhat cachectic and distressed. His vitals are normal, and physical examination reveals a mildly tender lower abdomen, without signs of peritonitis. His complete blood count, chemistries, and urinalysis reveal his baseline anemia of chronic disease, but otherwise, his laboratory findings are normal. A plain radiograph (Fig. 28.1) shows a large stool burden, but no evidence of free air or dilated loops of bowel. Rectal exam reveals hard stool in the vault, but no evidence of stool impaction. The patient is gently hydrated and treated with a soapsuds enema, which successfully leads to a bowel movement in the emergency department and relief of symptoms. He is discharged home uneventfully.

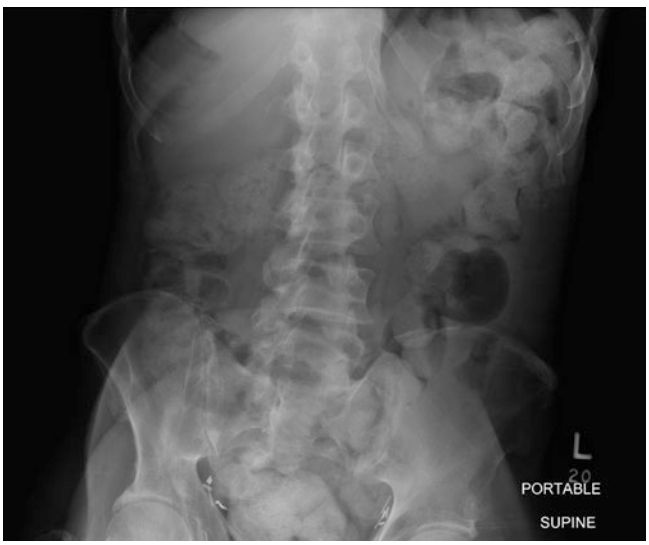

Fig. 28.1 Large amount of stool in upright abdominal radiograph

Introduction

Constipation is a common gastrointestinal symptom that varies widely in severity. Although definitions vary, constipation is generally characterized by the slow movement of feces through the intestines with fewer bowel movements than normal [1, 2]. Constipation may be transient and easily treated or cause major impairment and be resistant to multiple interventions, among both the general population and those with cancer. It is often underappreciated and undertreated in patients with cancer, and it has been reported to affect up to 50% of patients with advanced cancer [3].

Its reported prevalence varies from 1% to 81%. Such wide variation results from nonspecific definitions and differing base populations [2, 4–8]. More specifically, the prevalence of constipation among cancer patients ranges from 30–90%, and increases with age, opioid therapy, hospitalization, and need for palliative care [1, 9]. Age-related increases in constipation occur in the setting of immobility, dehydration, polypharmacy, and with advanced age, a reduced urge to defecate [1]. Among cancer patients receiving palliative care, those under 60 years of age reported a 33% prevalence of constipation, rising to 55% among those 70 years or older [10]. In one cross-sectional study of 520 cancer patients receiving strong opioids, 321 (61.7%) patients were assessed as constipated using a validated constipation questionnaire, while by physicians' subjectively judgment, 438 (85.7%) were constipated [11].

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Emergency department (ED) visits related to constipation are common both in the general and cancer population. Highlighting the healthcare burden of constipation, Sommers et al. found that of 131,048,605 total US ED visits in 2011, over 700,000 were related to constipation [12]. In 2019, of 28,424 total patient visits to the MD Anderson Cancer Center ED in Houston, Texas, 15,289 (54%) visits included a diagnosis related to constipation (unpublished data).

ED visits for constipation entail large and increasing healthcare expenditures. US ED visits for constipation increased by 41.5% between 2006 and 2011, from 497,034 to 703,391 visits, while the national cost of constipation visits increased from $733 million to $1.6 billion (in 2014 dollars) [12]. In the United Kingdom, cost to the National Health Service for treatment of constipation in the year 2017–2018 was estimated to be 162 million pounds and on average, 196 people were admitted to the hospital daily during the same time period. In addition, millions of dollars are spent annually on laxatives and primary care visits [8, 13–15].

In addition to healthcare costs, constipation-related symptoms are distressing and debilitating for those with cancer. Stigma and shame may prevent the patient from disclosing constipation symptoms to loved ones or healthcare providers [8, 13].

The Rome Diagnostic Criteria

Due to lack of overarching operational definitions for functional bowel disorders, an international group of gastroenterologists convened in 1988 in Rome, Italy to develop consensus criteria for the diagnosis of irritable bowel syndrome. This led to further attempts to develop systematic nomenclatures for a number of symptom-based functional gastrointestinal (GI) disorders. With an expanding research base, these taxonomical efforts were increasingly supported by physiologic data [16]. To date, Rome diagnostic criteria have become the gold standard for defining a number of functional GI disorders, including constipation. Despite accepted Rome criteria, there is limited agreement between generalist clinicians, expert specialists, and the public in recognizing and differentiating constipation from other functional GI disorders and nonpathologic symptoms. Experts recognize the need to align Rome diagnostic criteria with those symptoms that patients perceive to be important and functionally disabling [17].

The Rome diagnostic criteria categorize functional bowel disorders into five syndromes: irritable bowel syndrome, functional constipation, functional diarrhea, functional abdominal bloating/distention, and unspecified functional bowel disorder. Functional constipation is the most common form of constipation. A diagnosis of functional constipation per the Rome IV criteria requires that symptoms must be present for the last 3 months, with an overall onset of symptoms 6 months prior to diagnosis (Table 28.1). The Rome IV criteria include a new sixth category, opioid-induced constipation (OIC), particularly relevant to cancer patients [18]. OIC is defined as new or worsening constipation when initiating, changing, or increasing opioid therapy. While OIC is considered an adverse effect of opioids rather than a functional bowel disorder, the two often coexist. To meet OIC criteria, patients must experience two or more of the symptoms that define functional constipation with the same frequency cut-off of 25%. The Rome IV criteria also address narcotic bowel syndrome (NBS). NBS was first described over 25 years ago as a chronic or frequently occurring paradoxical development of, or increase in, abdominal pain associated with increasing doses of opioids [18–21].

Table 28.1 Rome IV criteria for functional constipation [18]

Duration of 3 months and symptom onset at least 6 months prior to diagnosis	
1	Presence of ≥2 of the following: Lumpy or hard stools in >25% of defecations Straining during >25% of defecations Sensation of anorectal obstruction/blockage for >25% of defecations Sensation of incomplete evacuation for >25% of defecations Using manual maneuvers such as digital manipulation or pelvic floor support to facilitate >25% of defecations <3 spontaneous bowel movements per week
	and
2	Loose stools rarely present without the use of laxatives
	and
3	Insufficient criteria for irritable bowel syndrome

Pathophysiology

Constipation can be attributed to primary causes such as colonic or anorectal dysfunction or secondary causes such as organic disease or medication use [20]. A number of factors are associated with constipation, including, but not limited to, dietary habits, genetic predisposition, absorption ability, colonic motility, daily behaviors, medication use, spinal cord compression or injury, musculoskeletal disorders such as muscular dystrophy, and external colonic compression (e.g., peritoneal tumors) [7].

Secondary constipation is often adverse effect of chemotherapeutic agents and medications used to treat concomitant diseases and symptoms. Constipation has been cited as the third most common symptom associated with chemotherapy administration [22]. A number of other drug classes cause constipation by reducing smooth muscle contractility (e.g., calcium channel antagonists, antihistamines, antidepressants) [7, 20]. Refer to Table 28.2 for a more comprehensive list of medications causing constipation.

Table 28.2 Common medications causing constipation

Drug class	Example of drug
Alpha-2 agonists	Clonidine, methyldopa
Calcium channel blockers	Verapamil, nifedipine
Tricyclic antidepressants	Doxepin, amitriptyline
Metal ion-containing agents	Iron, aluminum, bismuth, calcium
Opioids	Morphine, fentanyl, hydromorphone
Cannabinoids	Tetrahydrocannabinol (THC)
Antiulcer agents	Sucralfate, antacids
Anti-Parkinson drugs	Methyldopa
Antiepileptics	Phenytoin, carbamazepine
Antipsychotics	Clozapine, olanzapine, quetiapine
Antihistamines	Diphenhydramine, cetirizine
Antispasmodics	Dicyclomine and hyoscyamine
Anticholinergics	Belladonna, rasagiline
5-HT3 receptor antagonist	Ondansetron
Chemotherapeutic agents	Cyclophosphamide, vincristine
Nonsteroidal anti-inflammatories	Toradol, ibuprofen
Bile acid sequestrants	Cholestyramine

Chemotherapy-induced constipation is not well understood, but it is believed that it stems from the effects of the chemotherapeutic agent on nerve endings of the GI enteric nervous system. It is suggested that subtle changes in the enteric nervous system lead to abnormal colonic motor function, prolonged colonic transit time, infrequent bowel movements, and thus, constipation [22].

Opioids reduce bowel motility by binding to specific μ, δ, and κ receptors in the GI tract. Under normal circumstances, these receptors influence fluid and electrolyte transport in the stomach, ileum, and proximal colon, as well as promoting motility. Opioids bind to the μ receptor and lead to a decrease in peristaltic activity as well as reduction in mucosal secretions, ultimately causing decreased intestinal fluid absorption, slowed gastric emptying, and delayed intestinal traffic. Opioids also can weaken the susceptibility of rectal dilation to stimulation, reducing contractility as well as increasing sphincter tone [7, 22–25].

Narcotic bowel syndrome (NBS) is an entity deserving special mention as emergency physicians treating cancer patients may frequently encounter this condition. Pain is one of the most common complaints in the cancer population presenting to the ED and up to 60% of those patients are treated with opioids [26]. With continued opioid use, a paradoxical worsening of abdominal pain can occur despite increased opioid dose. Although the pathophysiology is not fully understood, NBS is thought to be related to heightened pain sensitivity localized to the GI tract. Chronic opioid use can cause neuronal changes that may lead to hyperalgesia. Other mechanisms include interactions with *N*-methyl D-aspartate receptor at the level of the spinal cord, increase in substance P synthesis, interaction with transmembrane G proteins, which have both inhibitory and excitatory effects on sensory neurons, increase in the endogenous opioid peptide dynorphin, which in turn leads to increased pain signaling at the level of the spinal cord, and neuroinflammation resulting in hyperalgesia [21, 27].

Finally, spinal cord compression or injury may cause spasticity in the muscles of the GI tract. Neurogenic bowel dysfunction can be characterized by increased colonic and anal sphincter tone if the compression or injury is above the conus medullaris [28].

Clinical Presentation

Cancer patients with constipation present with an array of symptoms. Given the range of pathophysiology associated with cancer and its treatment, it is imperative that the emergency physician not overlook a more urgent condition that may mimic constipation. The history of present illness should include duration of symptoms, history of similar symptoms, consistency and frequency of stools, sensation of blockage or a feeling of incomplete evacuation, straining, recent dietary changes and recent medication changes, or increase in opioids. A thorough past medical history, to include comorbidities such as diabetes, diverticulitis, past surgeries, and current medication usage, should be elicited [7]. A recent increase in cancer pain, requiring increase in opioids is often an important aspect of the history, thus the pain level should also be recorded.

Patients with NBS may describe a burning or colicky pain that is exacerbated by eating, progressive, and associated with nausea, vomiting, abdominal distention, and bloating [21, 27]. Cancer patients presenting to the ED with NBS are often difficult to diagnose and consultation with their oncologist or continuity physician may be helpful. The diagnostic criteria for NBS are shown in Table 28.3.

Symptoms of abdominal pain, bloating, nausea, inability to pass stool, small stools, straining, rectal pain, urinary retention, and overflow diarrhea are commonly present. More alarming findings such as change in bowel habits, weight loss, anemia, not passing flatus, vomiting, bloody

Table 28.3 Diagnostic criteria for narcotic bowel syndrome [21]

1	*Chronic or frequently recurring abdominal pain that is treated with high dose opioids (acutely or chronically)*
	and
2	Presence of at least three of the following:
	The pain worsens or incompletely resolves with continued or increasing doses of opioids
	There is worsening of pain when the opioid dose wanes and improvement when the opioids are reinstituted
	There is progression of the frequency, duration, and intensity of pain episodes
	The nature and intensity of the pain is not explained by a current or previous GI diagnosis

stools, history of inflammatory bowel disease, or history of colon cancer should prompt an expedited workup. Lower extremity weakness or numbness with urinary retention or in the setting of constipation should be further investigated to ensure there is no cord compression.

The Bowel Function Index three-item tool can be used for screening for opioid-induced constipation. This tool can be administered by the physician at the bedside and it consists of the patient's assessment of easiness of defecation in the last 7 days, the feeling of incomplete bowel evacuation during the last 7 days, and the patient's subjective judgment about the presence of constipation during the last 7 days [29].

Examination

Examination should begin with an evaluation for systemic toxicity. Does the patient appear acutely ill? Does the patient need acute resuscitation? It should then be followed by careful inspection of the abdomen, taking notice of the contour and movements of the abdomen as well as observing for symmetry. Inspection should be followed by auscultation, which can provide information about bowel motility. It is important to listen before palpating the abdomen as palpation can alter the frequency of bowel sounds. Next, palpating the abdomen will help with distinguishing masses, stool, a distended bladder, or signs of peritoneal inflammation. A digital rectal examination may be performed to check for stool impaction and sphincter tone. A history of bloody stools should prompt an examination for hemorrhoids or anal fissures. However, rectal exam in the oncologic population should be postponed until there is evidence that the patient is not neutropenic.

After a focused examination of the abdomen, a more thorough examination may be done in search of other systemic causes of constipation, such a hypothyroidism, hypercalcemia, spinal cord compression, and dehydration.

Differential Diagnosis

The first step in the diagnostic approach is to form a broad differential to ensure more serious causes are not missed. Differential diagnosis possibilities should include the following:

1. *Bowel Obstruction:* Bowel obstruction (small or large) can be caused by scar tissue, hernias, and malignancy. Patients presenting with bowel obstruction can present with severe pain, fever, bilious or nonbilious vomiting, bloating, and obstipation. However, patients can also present with variable, nonclassical symptoms. Having a history of mass in the GI tract, prior surgery, or abdominal hernias may further point to a bowel obstruction. Clinically, patients may appear ill, have a distended abdomen that is often tympanic with decreased or increased bowel sounds, and may be diffusely tender with or without signs of peritoneal irritability. In this case, a supine and upright radiograph may demonstrate distended loops of bowel or air-fluid levels indicating possible obstruction. A CT of the abdomen should be obtained to better evaluate and delineate the cause of obstruction [30]. If the diagnosis is missed, bowel obstructions can progress and cause bowel ischemia.
2. *Bowel Perforation:* Bowel perforation is a surgical emergency. There are multiple etiologies, but commonly neoplasm, diverticulitis, abscesses, inflammatory and infectious colitis, as well as bowel ischemia should be considered as causes of perforation. Stercoral colitis (Figs. 28.2 and 28.3) is a rare complication due to fecal impaction leading to increased intraluminal wall pressure, inflammation, and distention of the colon, which in turn leads to ischemic pressure and necrosis with ulceration and perforation. It can result in peritonitis and rapidly progress to septic shock. Neutropenic colitis may also cause transmural necrosis and perforation if severe. These patients will often present with severe pain, abdominal distention, nausea, and/or vomiting and possibly obstipation or diarrhea, depending on the etiology. On physical examination, the patient appears ill and may exhibit findings consistent with peritonitis. Workup

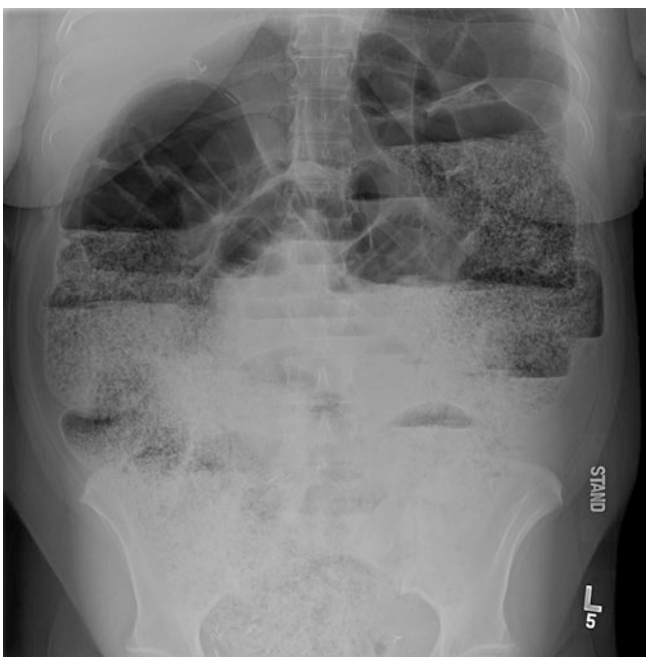

Fig. 28.2 Plain radiograph demonstrating air-fluid levels and a distended bowel in a patient with impacted fecal material

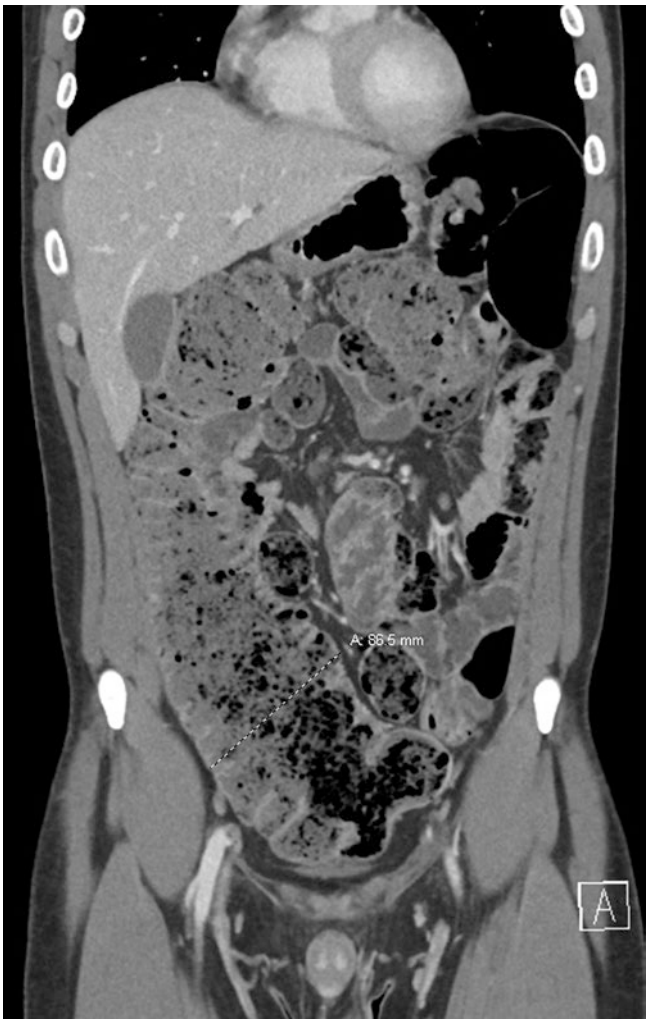

Fig. 28.3 Stercoral colitis in a patient with impacted fecal material

should include an emergent upright chest radiograph to evaluate for free air under the diaphragm. However, if plain radiography is negative, a CT of the abdomen should be immediately obtained, as plain radiographs have only a sensitivity of 50–70% in detecting extraluminal air [31].

3. *Malignant Spinal Cord Compression:* Malignant cord compression is an oncologic emergency and a potentially devastating condition, that if missed can lead to catastrophic neurological deficits. The condition has been reported to occur in approximately 5% of all cancer patients and up to 20% of the time, it is the initial manifestation of cancer [32]. Its incidence in advanced cancer has been reported to be approximately 15% [33]. Constipation may be the initial presenting symptom. A thorough history of present illness and review of systems may allow an early diagnosis. Neurological symptoms may include extremity weakness, numbness, and tingling. Symptoms such as urinary retention or overflow incontinence are also important red flags. Known bony metastatic disease increase the likelihood of cord compression and thorough questioning about back pain and changes in pain intensity may be helpful. The neurological exam may be normal in the early stages of cord compression. Rectal tone should be checked, if the patient is not neutropenic. If malignant spinal cord compression is suspected, an emergent magnetic resonance imaging study of the spine is indicated with concomitant initiation of systemic steroids.
4. *Diverticulitis:* This condition can often present subtly, but if missed can cause complications such as phlegmon formation and perforation. The patients may present with fever and lower abdominal pain. Nausea and/or vomiting may be present or absent and the patient may give a history of diarrhea or constipation. Exam will often show tenderness of the left lower quadrant and the diagnosis can be confirmed with CT scan of the abdomen. The patient may or may not have an associated leukocytosis.
5. *Hypothyroidism:* While most cases of hypothyroidism are due to a primary process in the thyroid, a small percentage are due to other causes, such as neoplasm and medications (e.g., chemotherapeutic agents and immunotherapy). Patients may present with subtle symptoms including constipation, fatigue, muscle cramps, weight gain, voice changes, dry skin, and cold sensitivity. In these patients, again a thorough history is important as is a detailed review of systems. Exam may reveal a goiter, dry skin, pretibial edema, and delayed relaxation of deep tendon reflexes. Checking a serum thyrotropin level (TSH) is the single best screening test for primary thyroid dysfunction, but not adequate for hospitalized or acute ill patients [34]. Additional testing of for free thyroxine levels (T4) as well as triiodothyronine (T3) may assist the diagnosis.
6. *Hypercalcemia of Malignancy:* One of the most common causes of hypercalcemia is malignancy, affecting approximately 30% of patients with cancer at some point. Hypercalcemia may be due to bony metastasis or secretion of parathyroid hormone-related protein. Cancers with higher risk of hypercalcemia are multiple myeloma, renal cell carcinoma, lung, breast, and colorectal cancers. Drugs such as tamoxifen can also cause hypercalcemia. The patient may present with nonspecific complaints such as fatigue, anorexia, constipation, nausea, and abdominal pain. They may also present with pancreatitis and exhibit an elevated lipase, or nephrolithiasis with renal insufficiency. Clinically, the patient may appear dehydrated, lethargic, or even confused, but more often the physical exam is nonspecific. High blood pressure, bony tenderness, lower extremity muscle weakness, and tongue fasciculations may be seen. Workup should include chemistries with ionized calcium as well as liver

enzymes to include albumin, as up to 40% of calcium is protein bound. In this case, the constipation is secondary to the primary disease. An EKG should be obtained to check for QT interval shortening and Osborn or J waves and intravenous fluids initiated in the absence of contraindications [35].

Diagnosis

Assuming an adequate differential has been considered, constipation can be diagnosed simply by history and exam. In fact, the American College of Gastroenterology Chronic Constipation Task Force recommends against routine diagnostic testing in chronic constipation if there are no red flags [36]. However, the presence of cancer will often prompt further diagnostic testing.

In the ED, a complete blood count should be ordered to evaluate for neutropenia prior to performing a rectal exam. Chemistries to include electrolytes should be done to exclude metabolic causes of constipation. Thyroid function tests may be helpful if hypothyroidism is suspected. While imaging is not routinely required in the ED when uncomplicated constipation is suspected, an acute abdominal series radiograph with supine and upright views may reveal free air and air-fluid levels. If there are any red flags in the history suggesting a more serious process, computed tomography of the abdomen should be performed.

Treatment

Once it is determined that the patient has uncomplicated constipation and other emergent causes (e.g., bowel obstruction, spinal cord compression) ruled out, the next step prior to treatment is to determine whether constipation is primary or secondary. Primary constipation is due to intrinsic defects in bowel function and usually is considered only after secondary causes of constipation have been ruled out [20]. The cancer patient is likely to have constipation due to secondary causes, such as medication use, or the malignancy itself.

As constipation is often multifactorial, the treatments will vary. In general, multiple approaches should be employed. These begin with hydration of the patient if the clinical picture warrants it, as well as correction of abnormal electrolytes. Most cancer patients presenting to the ED have already attempted oral medications such as osmotic or stimulant laxatives that have failed to relieve the symptoms. Assuming home treatment has failed, the most common approach in the ED is the administration of enemas and suppositories, followed by oral laxatives. Another less appealing approach (for both physician and patient) is to perform rectal disimpaction.

If a high clinical suspicion exists for NBS as the cause of the constipation, is it imperative to avoid treatment with increasing opioids, although clinicians might be initially inclined to do so to control pain. Emergency physicians should consider that patients and providers alike often exhibit frustration due to negative evaluations and increased healthcare utilization by this cohort of patients. Unrecognized NBS can lead to an increase in opioid therapy worsening pain and repeated cycles of treatment failure. Treatment of NBS begins with detoxification, which will likely require hospital admission. Inpatient detoxification involves placing the patient on a continuous opioid drip while the amount is gradually reduced in a structured fashion. The goal of treatment is to achieve dose reductions of 10–33% per day, while providing anxiolytics during withdrawal. Other options for the emergency clinician are nonopioid pain modulators and anxiolytics. Further outpatient support will be necessary for these patients for behavioral modifications, psychological support, and pain management [21, 27, 37]. For opioid-induced constipation, the emergency physician may consider a peripheral acting μ-opioid receptor antagonist (PAMORA) [1].

Treatment of the elderly patient must be individualized based on other comorbidities such as kidney or heart disease. Saline laxatives should be used with caution in this group due to the risk of hypermagnesemia, while nonabsorbable dietary fiber and bulk agents should be avoided in nonambulatory, elderly patients due to the risk for mechanical obstruction. Osmotic laxatives such as polyethylene glycol are a good option for the elderly, but will not likely cause a bowel movement for 2–3 days [1].

In the next section, we will discuss pharmacologic agents in detail.

Pharmacological Agents in the Treatment of Constipation

Bulk-Forming Laxatives

These are often used as first-line agents in patients with chronic constipation and those who cannot take adequate fiber. Examples of bulk-forming laxatives are psyllium (Metamucil), wheat dextrin (Benefiber), methylcellulose (Citrucel), and polycarbophil (Fibercom). The goal of fiber therapy is to trap water in the GI lumen, which in turn stimulates colonic motility and increases frequency of bowel movements. Abdominal bloating is a common adverse effect. These agents are not adequate to treat constipation in the ED and should be considered preventative therapy [1].

Stool Softeners and Lubricants

Examples include mineral oil and docusate sodium. These agents have detergent-like properties that help lubricate the stool by increasing water content and are often tried by the patients prior to ED presentation. They are most likely to work in those with occasional or short duration constipation, and less likely to work in the acute setting or with fecal impaction [1].

Osmotic Laxatives

This class includes saline laxatives such as magnesium citrate and milk of magnesia, as well as poorly absorbed sugars such as lactulose, sorbitol, and polyethylene glycol. Their mechanism of action is to induce water movement into the GI lumen and therefore increase bowel movement frequency by means of softening the stool and increasing volume. Osmotic laxatives are frequently used in the ED as initial treatment for uncomplicated constipation; however, there are instances in which they should be avoided. Due to the potential for electrolyte absorption, saline laxatives are not recommended for patients with renal or cardiac insufficiency. Poorly absorbed sugars, such as lactulose, can lead to abdominal bloating and flatulence, limiting its use due to poor tolerability. Finally, polyethylene glycol is an option, when other therapies have failed if the patient can tolerate oral intake [1].

Stimulant Laxatives

Included in this class are drugs such as bisacodyl, senna, sodium picosulfate, and aloe. These work by increasing intestinal secretions and promoting neurotransmitter release, increasing colonic motility. This class is less helpful in the acute setting but are generally well tolerated with minimal side effects [38].

Enemas

Commonly used enemas include Fleet, soapsuds, and milk and molasses enemas. While these can be very effective in the acute setting, they can also cause severe adverse events (e.g., perforation, metabolic derangements) and as such should be applied carefully [39]. Enemas are contraindicated in those with neutropenia or thrombocytopenia, paralytic ileus, intestinal obstruction, recent colorectal or gynecological surgery, rectal trauma, toxic megacolon, colitis, or recent radiotherapy in the abdominopelvic area [1].

Newer Agents

These include the secretagogues and peripheral acting μ-opioid receptor antagonists (PAMORAs). OIC can be treated with both lubiprostone (a secretagogue) and PAMORAs, such as naloxegol and methylnaltrexone. PAMORAs selectively and competitively bind to the peripheral acting μ-opioid receptors in the enteric nervous system. All PAMORAs have shown effectiveness in treating OIC.

Naloxegol was the first orally dosed PAMORA for the treatment of OIC. It is a PEGylated derivative of naloxone. The recommended dose is 25 mg daily, which may be reduced if patient becomes symptomatic. It is generally well tolerated and will produce a bowel movement in most patients with OIC in approximately 1 week. There are no significant and severe associated adverse events and no reduction in analgesia [1, 25]. It is recommended that other laxatives are discontinued when taking naloxegol and other PAMORAs to decrease adverse side effects such as bloating [40].

Methylnaltrexone is a fast-acting PAMORA, derivative of naltrexone, that is administered subcutaneously and may be useful in the ED [38]. Most patients achieve defecation within 90 minutes of administration. Treatment has not been reported to impact pain control or precipitate opioid withdrawal [1, 41]. Although there is a theoretical risk of perforation among patients with structural abnormalities of the bowel wall, a recent review of 333 adults and children with peritoneal carcinomatosis receiving methylnaltrexone for the treatment of OIC found only one perforation [42].

Naldemedine is an oral PAMORA that has been reported to produce a spontaneous bowel movement in about 16 hours. Naldemedine has no effect on analgesia and there is no increase in opioid withdrawal symptoms [41]. The most effective dose to manage OIC is 0.2 mg [1, 41, 43].

Lubiprostone is a secretagogue that activates type-2 chloride channels in the intestine allowing for an increase in liquid contents and promoting spontaneous bowel movements [25].

Disposition

If the patient is nontoxic appearing and appears to be responding well to the interventions in the ED, they may be discharged with close follow up. However, patients with advanced cancer or unmet palliative care needs may require admission for symptom control or monitoring for complications. Similarly, patients who appear dehydrated, cannot take adequate oral intake, have uncontrolled pain, or constipation that is not resolving must be admitted.

Prevention and Patient Education

Dietary and lifestyle modifications should be encouraged at every visit with the oncologist, as well as discussed during discharge from the ED. Increasing water and fiber content is a simple preventive measure, however, it is a difficult task for some cancer patients due to appetite loss. Probiotics can help as gut microbiota plays a significant role in the GI motility. However, while these recommendations are generally given, the data to support their efficacy are limited [38]. At a minimum, when prescribing opioids for the cancer patient, the clinician should discuss the issue of complication and initiate a bowel regimen.

Conclusion

Constipation in cancer patients offers a specific set of challenges that emergency physicians will need to be familiar with. To improve quality of life in the cancer patients suffering from constipation, more research and data will be needed to further align patient's perception of constipation, clinician's practice, and clinical guidelines. Agreement on a unifying definition can help with earlier recognition and treatment of the disturbing GI symptoms and help reduce morbidity and distress. Questionnaires in existence can be further improved for usability in the ED and to make effective decisions with regard to the best treatment for the chronic constipation patient in the acute setting. Continued education of ED clinicians on the management and opioid-induced constipation and narcotic bowel syndrome is important in the care of cancer patients who often use narcotics. This can help reduce patient distress and increase understanding, which can help the doctor-patient relationship that is often fractured by these patients with difficult clinical presentations and increased healthcare utilization. Increased awareness of NBS by all clinicians can be helpful to these patients as they often need a multidisciplinary team approach including inpatient and outpatient care. In closing, continuing education efforts can greatly help improve the cancer patient's quality of life and help clinicians address the specific set of challenges associated with this cohort.

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Endocrinology and Metabolism

29

Sai-Ching Jim Yeung

Introduction

Routine clinical chemistry analyses including electrolyte and metabolic panels are frequently ordered as part of an emergency department (ED) evaluation to identify abnormalities in electrolyte or acid-base imbalance and to monitor treatments of known abnormalities. In cancer survivors and patients with active malignancies presenting for emergency care, abnormalities in the electrolyte and metabolic panel are very common. Moreover, while serum magnesium is very often not part of the electrolyte and metabolic panel in many EDs, it should be routinely checked in cancer patients because hypomagnesemia is highly prevalent in this population.

In addition to "reflex" treatments in the ED to normalize electrolytes and glucose, early diagnosis or initiation of the diagnostic work-up to identify the underlying cause of the abnormalities will minimize morbidity and mortality as well reduce costs of care. In general, the past medical, medication, and dietary histories will help to determine the cause of abnormalities. A synthesis of physical examination findings with the histories will give clues to specific clinical syndromes.

Case Study

A 65-year-old male previous heavy smoker with chronic obstructive pulmonary disease was recently diagnosed with stage 4 squamous cell lung carcinoma. He had received his third cycle of pembrolizumab and carboplatin plus paclitaxel 11 days ago. He presents with the complaint of palpitations that woke him up this morning. He felt that his heart was racing and would not slow down with rest. He was brought to the ED by ambulance. On arrival, his heart rate was 160/min. His systolic blood pressure was 100 mmHg. He was otherwise at his baseline condition. Stat cardiac monitoring and electrocardiogram showed atrial fibrillation with fast ventricular response. Metoprolol 10 mg was given stat intravenously and was repeated after 15 minutes. The heart rate was controlled at about 100/min. The heart rhythm remained atrial fibrillation. Serum chemistry showed that potassium was 3.3 mEq/L and serum magnesium was 1.4 mg/dL. Potassium chloride and magnesium sulfate infusions were initiated to correct electrolyte abnormalities. Thyroid function tests were sent to the lab, and later TSH was reported to be <0.001 mU/L, with a free thyroxine of 3.0 ng/dL. Cardiology was consulted and evaluation did not reveal underlying atherosclerotic heart disease. Elective cardioversion was performed, and he was successfully converted back to sinus rhythm.

His thyrotoxicosis was due to anti-PD1 antibody-induced thyroiditis and managed with beta-adrenergic blockade. The patient required close follow-up as the thyrotoxic state could resolve, and metoprolol might need to be discontinued. The clinical course of immune thyroiditis may result in hypothyroidism after the thyrotoxic phase, and the patient would then need thyroid hormone replacement.

Metabolic Emergencies

Hypernatremia

Hypernatremia results from loss of balance between sodium and water: excess sodium intake, low water intake, high water loss, and changes in renal reabsorption of water and/or sodium.

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Causes:

- Inadequate water intake: obstruction of the gastrointestinal tract, treatment-induced nausea and vomiting, and treatment-induced mucositis. A debilitated bed-bound cancer patient may not have free access to water. Primary hypodipsia is loss of thirst due to abnormality in the supraoptic nucleus of the hypothalamus caused by a primary or metastatic malignancy or treatment (surgery or radiation) of a central nervous system tumor.
- Increased water loss: diuretic use, high fever, burns, or diarrhea.
- Iatrogenic causes: inappropriate intravenous (IV) fluid administration, total parenteral nutrition, and dialysis.
- Diabetes insipidus:
  1. Central: Caused by changes affecting the anterior pituitary or related hypothalamic nuclei (e.g., neurosurgery, destruction by tumors, hemorrhage, head injury, infarction, and infection).
  2. Nephrogenic: Most familial nephrogenic diabetes insipidus cases are caused by mutations of the V2 receptor mutations or aquaporin-2 water channel. However, these are rare among cancer patients. Acquired nephrogenic diabetes insipidus can result from some common drugs (e.g., demeclocycline, lithium, foscarnet, clozapine, amphotericin, glyburide, colchicine, acetohexamide, tolazamide, and methoxyflurane) and chemotherapy agents (e.g., ifosfamide, vinblastine, and streptozocin).

Symptoms The clinical manifestations of hypernatremia are primarily related to cellular dehydration leading to central nervous system dysfunction and are more pronounced with a high level or a fast rate of increase. Thirst is frequently the first symptom. Muscle weakness and central nervous system changes (restlessness, weakness, and lethargy) are usually not manifested until the sodium level is >160 mEq/L, and at this point, the patient may become comatose. Diabetes insipidus is characterized by polyuria, urine hypo-osmolality, and polydipsia. Symptoms of intravascular volume depletion may appear if water loss exceeds water intake.

Diagnosis The cause of hypernatremia is usually evident by history alone. Accurate measurement of fluid intake and output is helpful. A water deprivation test may differentiate between central and nephrogenic diabetes insipidus. Urine osmolality and urinary sodium concentrations should be measured. A serum uric acid >5 mg/dL with polyuria and polydipsia is suggestive of central diabetes insipidus.

Management:

- Total body water deficit can be estimated as 0.6 × (body weight in kg) × ((serum sodium level/140) − 1). In patients with acute hypernatremia, free water can be replaced rapidly. In patients with chronic hypernatremia, the serum sodium level should be decreased by <2 mEq/L/hour until the symptoms resolve. The remaining water deficit can be corrected in 48 hours.
- Give water enterally, or infuse IV solutions low in sodium (e.g., 0.2% NaCl or dextrose 5% in water).
- Central diabetes insipidus usually is treated with various dosage forms of desmopressin (DDAVP) (5–20 μg intranasally every 12 hours, 1–2 μg subcutaneously once a day, or 0.1–0.2 mg orally twice a day).
- Nephrogenic diabetes insipidus may be managed with a low-salt diet and thiazide diuretics to induce natriuresis and/or indomethacin. Drugs that contribute to nephrogenic diabetes insipidus should be discontinued if possible.

Hyponatremia

Multiple (integumentary, gastrointestinal, cardiovascular, renal, and nervous) organ systems are integrated into regulatory networks for homeostatic control of intravascular volume and serum osmolality, and perturbations of these regulatory networks in patients by cancer or cancer treatments frequently cause hyponatremia.

Causes:

- Risk factors for hyponatremia include chemotherapy, nausea and vomiting, hydration with hypotonic fluid, pain, opioids, and stress
- Hypothyroidism (see section about thyroid dysfunction below)
- Adrenal insufficiency (see section about adrenal dysfunction below)
- Congestive heart failure
- Cirrhosis
- Syndrome of inappropriate secretion of antidiuretic hormone (SIADH), characterized by normal or increased intravascular volume, low serum osmolality, and inappropriately high urine osmolality in the absence of diuretics, cirrhosis, heart failure, hypothyroidism, and adrenal insufficiency:
  1. Cancers secreting vasopressin (e.g., about 15% of SCLC, 1% of other lung cancers, and 3% of squamous cell head and neck cancers) [1]
  2. Abnormal secretory stimuli for ADH (e.g., intrathoracic infection, positive pressure ventilation)
  3. Cytotoxic chemotherapeutic agents affecting paraventricular and supraoptic neurons (vinca alkaloid [vincristine and vinblastine], high-dose cyclophosphamide)
- Renal salt wasting:
  1. Tumor-induced: Mediated by atrial natriuretic peptide [2]
  2. Drug-induced: Damage to the renal tubules and resulting defects in salt and water transport may be the major cause of hyponatremia associated with low-dose cyclophosphamide therapy [3] and platinum compounds [4]

Symptoms The signs and symptoms of hyponatremia include general weakness, fatigue, nausea, and vomiting, all of which are nonspecific. The severity of symptoms depends on the rate of decline and degree of hypo-osmolality. Significant symptoms usually appear as the serum sodium concentration falls below 120 mEq/L. Neurologic symptoms of headache, behavioral changes, lethargy, confusion, seizure, stupor, and coma may manifest, while progressive cerebral edema causes brain damage, brain stem herniation, respiratory failure, and death.

Identifying the causes of hyponatremia requires additional laboratory evaluations, including urinary sodium measurement, thyroid and adrenal function tests, and correlation with clinical history.

Diagnosis Figure 29.1 outlines the evaluation and treatment of hyponatremia. Evaluation of intravascular volume status is very important in diagnosing the underlying cause of hyponatremia. Hypotonicity must be confirmed by measuring osmolality. Pseudohyponatremia caused by hyperlipidemia, hyperproteinemia, severe hyperglycemia, and administration of hypertonic mannitol should be excluded.

Management:

- If the patient is not hypovolemic, free water intake may be restricted to 500–800 mL/day.
- There are several ways to increase free water excretion:
  1. Drug-induced nephrogenic diabetes insipidus (e.g., demeclocycline 600–1200 mg/day)
  2. Loop diuretics (e.g., furosemide 20–40 mg/day)
  3. Blockade of V2 receptors to promote free water excretion (aquaresis) (e.g., conivaptan, lixivaptan, tolvaptan, and satavaptan) [5]
- Fludrocortisone (0.1–0.6 mg/day) is a mineralocorticoid that may be used to decrease renal sodium excretion.
- For patients with hypovolemia, oral intake of sodium may be increased by sodium chloride tablets along with intravascular volume expansion by infusing normal saline (0.9% NaCl).
- For emergent cases of hyponatremia in which central nervous system symptoms are evident and significant, infusion of hypertonic saline (3% NaCl) at a rate of 1 mL/kg/hour may be indicated with close monitoring (in an intensive care unit).

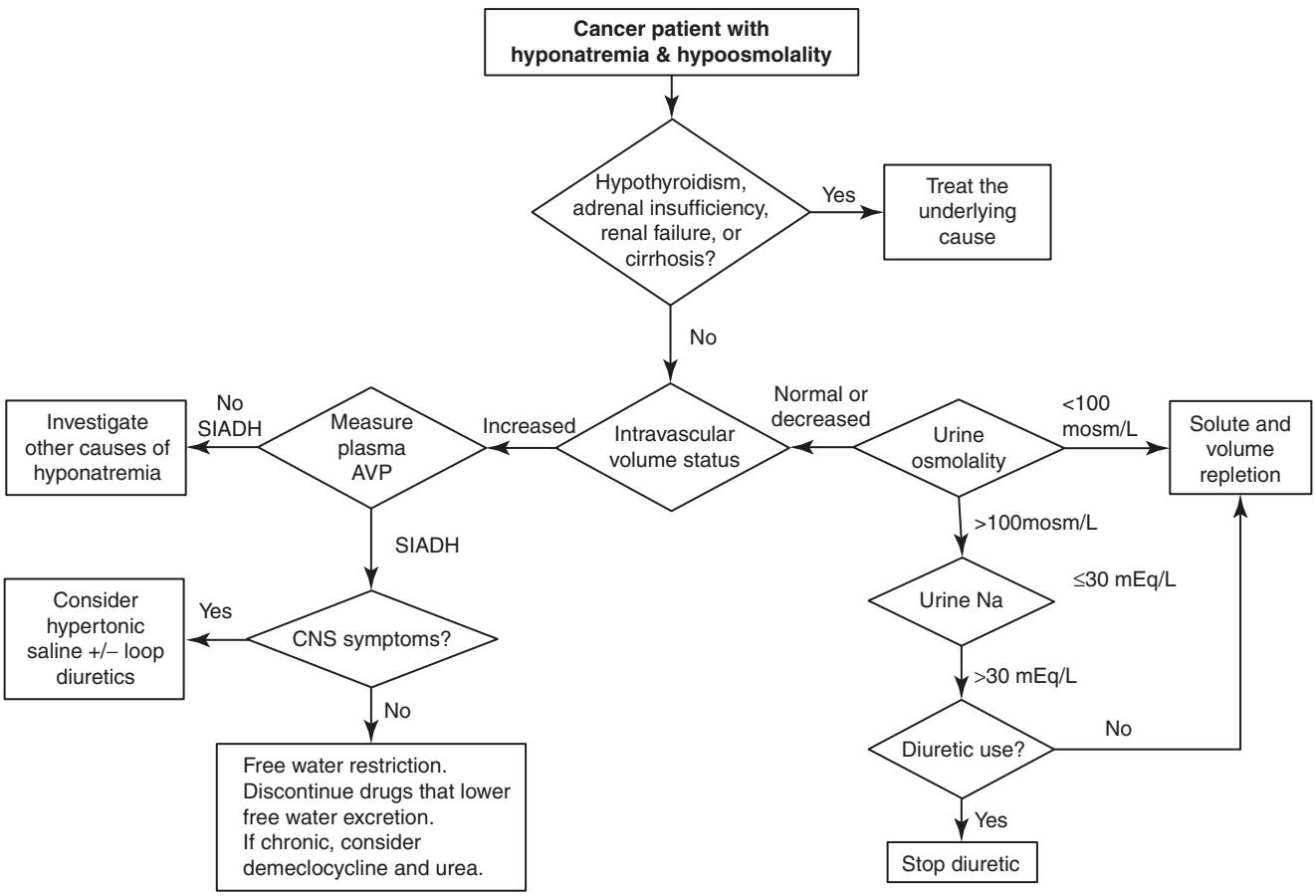

Fig. 29.1 Algorithm for the evaluation and management of hyponatremia

Hyperkalemia

In the absence of excessive intake of potassium, hyperkalemia is an electrolyte abnormality often associated with renal abnormalities in cancer patients.

Causes:

- Diminished renal excretion of potassium occurs in patients with acute or chronic renal failure, renal hypoperfusion, or type 4 renal tubular acidosis.
- Drugs that can lead to decreased potassium excretion include potassium-sparing diuretics and angiotensin-converting enzyme inhibitors.
- Excessive oral potassium supplementation and inappropriate potassium content in IV fluid or total parenteral nutrition.
- A significant release of intracellular potassium will cause hyperkalemia, as in the case of tumor lysis syndrome.
- Transcellular shifts of potassium may be seen in insulin deficiency, β-blocker therapy, and acidemia, elevating serum potassium levels.
- Drug-induced hyperkalemia often occurs with preexisting impaired renal excretion of potassium. The drugs commonly used by cancer patients that cause hyperkalemia include cyclosporin A, tacrolimus, heparin, mitomycin-C, and pentamidine.

Symptoms Severe clinical manifestations of hyperkalemia are usually absent until the serum level is >7.5 mEq/L. Some patients (e.g., those with chronic renal failure) can tolerate high serum potassium levels without having any clinical signs or symptoms. Hyperkalemia causes depolarization of excitable membranes. This membrane depolarization leads to the excitability of nerves and muscles, causing cramps, muscle weakness, and paralysis. At >7.5 mEq/L, nonspecific symptoms, such as muscle weakness, cramping and paralysis of different muscle groups, may occur.

Diagnosis The most vital organ with excitable membranes is the heart. Electrocardiogram (EKG) changes and potentially fatal arrhythmias may be present. An early EKG abnormality associated with hyperkalemia is peak T waves (Fig. 29.2) followed by progressive QRS widening to a "sinusoidal" wave (Fig. 29.3) [6]. Ventricular tachycardia, fibrillation, and asystole may occur.

Hypotension and hypoglycemia with hyperkalemia suggest possible adrenal insufficiency. Serum electrolytes, blood urea nitrogen, serum creatinine, urinalysis, urine electrolytes, and arterial blood gases will often elucidate the cause of hyperkalemia.

Management:

- If possible, discontinue medications that may contribute to hyperkalemia (e.g., potassium supplements, spironolactone, amiloride, β-adrenergic blockers, nonsteroidal anti-inflammatory drugs, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors).

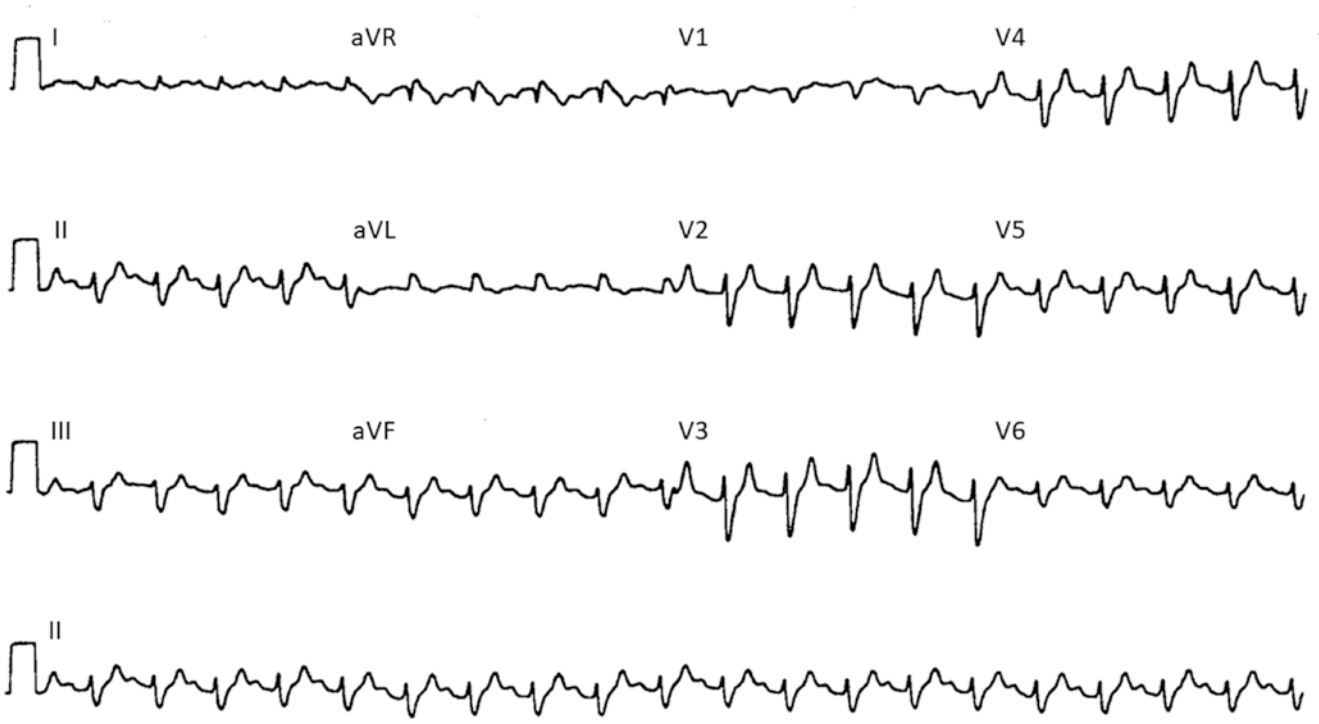

Fig. 29.2 Peaked T wave in an electrocardiogram of a hyperkalemic patient. The serum potassium was 7.3 mEq/L

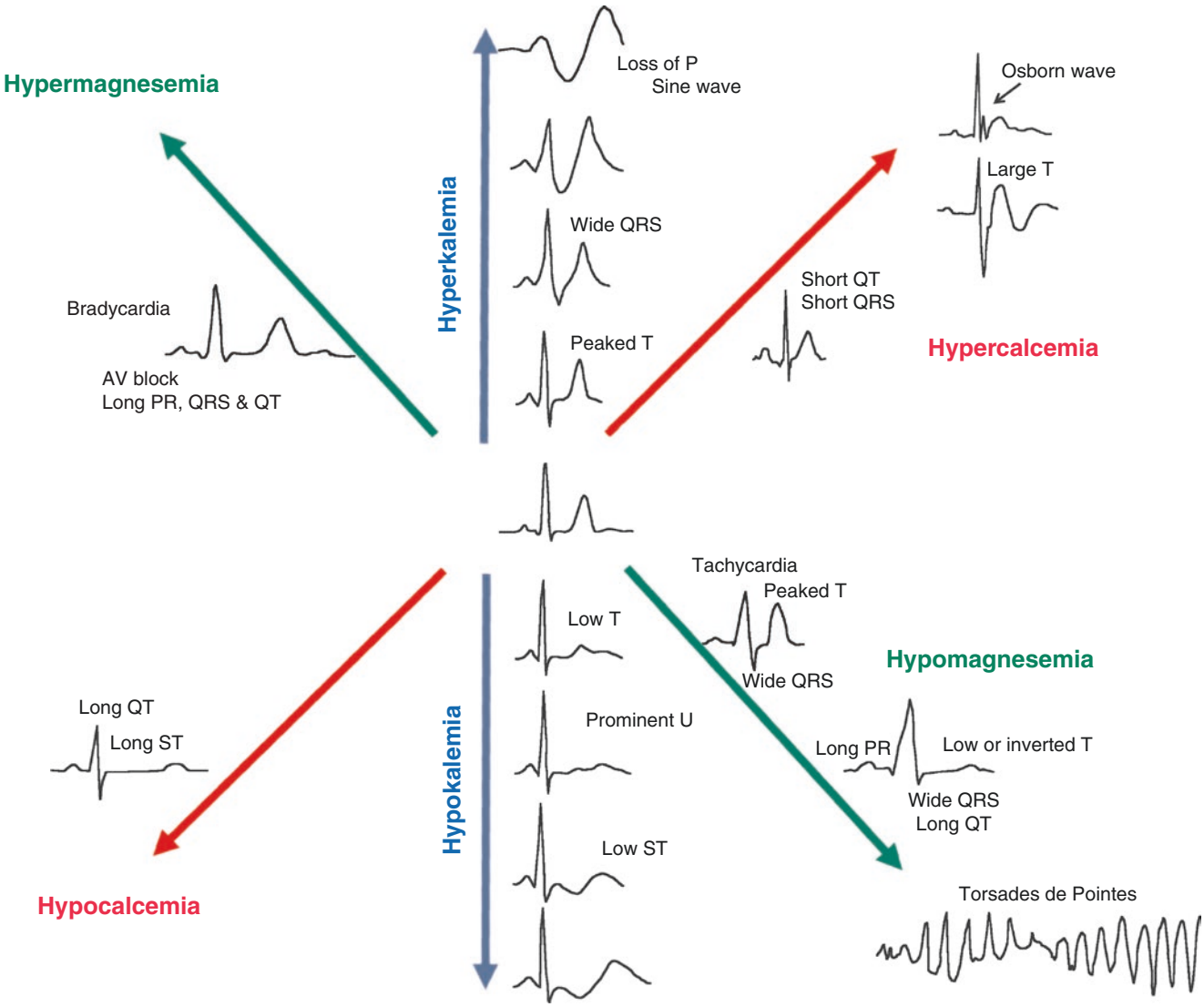

Fig. 29.3 EKG changes in the presence of electrolyte abnormalities [6]

- Hyperkalemia due to calcineurin inhibitors cyclosporine and tacrolimus may respond to treatment with fludrocortisone.
- For severe hyperkalemia (>6.5 mEq/L) and/or EKG changes, monitor EKG continuously and treat with the following:
  1. IV calcium (1–2 g of calcium gluconate or 0.5–1.0 g of chloride).
  2. IV sodium bicarbonate (1 mEq/kg).
  3. IV glucose (usually 25 g) plus 6–8 U of regular insulin.
  4. β-adrenergic agonists (e.g., albuterol 2.5 mg nebulized inhalation). Loop diuretics may be used to promote natriuresis and kaliuresis.
- Ion exchange resins, such as sodium polystyrene sulfonate (Kayexalate), which can be administered orally (15–30 g/dose) or rectally (30–60 g/dose) as a retention enema, may remove potassium from the body via the gastrointestinal tract.
- Emergent hemodialysis may be used in refractory cases.

Hypokalemia

Hypokalemia is a very common electrolyte abnormality in cancer patients.

Causes:

- Potassium intake in cancer patients may decrease for various reasons, such as nausea, vomiting, anorexia and gastrointestinal obstruction.
- Potassium may be lost from the gastrointestinal tract via vomiting or diarrhea, and from the kidneys as a result of intrinsic tubular defects and type 1 renal tubular acidosis.

- Drug-related effects (e.g., loop diuretics, aminoglycosides, cyclophosphamide, ifosfamide, carboplatin, cisplatin, and amphotericin B).
- Hypokalemia owing to excess mineralocorticoid activity may result from deregulated aldosterone production by adrenal tumors or other renin-secretion cancers [renal (Wilms tumor, renal cell carcinoma, or hemangiopericytoma), lung (SCLC, adenocarcinoma), hepatic, pancreatic, or ovarian carcinomas] [7].
- Exogenous corticosteroids, fludrocortisone, and Cushing syndrome, which includes ectopic secretion of ACTH by some cancers (e.g., small cell lung cancer [SCLC], carcinoid tumors).
- Alkalosis, either respiratory or, on a larger scale, metabolic, may precipitate hypokalemia via a transcellular potassium shift. Drugs that cause potassium redistribution include insulin, β-adrenergic agonists, theophylline, and chloroquine.

Symptoms Patients with mild hypokalemia (3.0–3.5 mEq/L) are usually asymptomatic. In those with severe hypokalemia (<3.0 mEq/L), symptoms may range from mild to severe (and potentially fatal). Cardiac manifestations range from flat T waves, T-wave depression, and prominent U waves to serious arrhythmias (ventricular tachycardia or fibrillation) (see Fig. 29.3). Neurologic manifestations include muscle weakness, paresthesia, and paralysis.

Diagnosis Medications and dietary histories will help determine the cause of hypokalemia. Physical examination will give clues regarding Cushing syndrome. Measurement of serum electrolytes, including magnesium, blood urea nitrogen, and creatinine; urinalysis; and urine electrolyte measurement will help to diagnose renal potassium loss.

Management The oral route for potassium replacement is preferred over other routes if feasible. The IV route may be used in patients with severe hypokalemia or those unable to tolerate enteral replacement. The rate of IV administration should not exceed 20 mEq/hour diluted in IV fluid through a peripheral vein. The infusion rate may be as high as 40 mEq/hour through a central venous catheter. In general, the relationship between the degree of hypokalemia and total body deficit is linear. For each 1 mEq/L decrease in serum potassium level, the total body deficit would be about 300 mEq. This total body deficit may be corrected over days. Almost half of the cancer patients with hypokalemia have concurrent hypomagnesemia. Potassium-sparing diuretics, such as amiloride and spironolactone, inhibit potassium excretion and may have a role in decreasing renal potassium wasting.

Hypermagnesemia

Hypermagnesemia is uncommon.

Causes:
- Renal failure.
- Increased intake of magnesium in the presence of renal insufficiency.
- Excessive magnesium in IV fluid or parenteral nutrition.
- In the absence of renal insufficiency, hypermagnesemia owing to excessive intake of magnesium is very rare, as excess magnesium in the gastrointestinal tract leads to diarrhea.

Symptoms The clinical manifestations of hypermagnesemia correlate well with the serum level of magnesium. Early signs include nausea, vomiting, weakness, and cutaneous flushing, which can occur when the serum magnesium level is greater than 3 mg/dL. With levels greater than 4 mg/dL, hyporeflexia and loss of deep tendon reflexes may occur. At levels greater than 5 mg/dL, hypotension and EKG changes (QRS widening, QT and PR prolongation, and conduction abnormalities) may occur (see Fig. 29.3). Respiratory depression, coma, and complete heart block may occur at levels greater than 9 mg/dL. Asystole and cardiac arrest occurs at levels greater than 10 mg/dL.

Diagnosis Excessive magnesium intake usually is evident in the patient's dietary and medication histories. Renal function should be assessed by measuring blood urea nitrogen and serum creatinine.

Management:
- Medications and IV fluids containing magnesium should be discontinued.
- Patients with mild symptoms and normal renal function can be observed without intervention.
- Magnesium excretion can be accelerated by hydration with crystalloid fluid and loop diuretics.
- In severe cases with hypotension and/or cardiac arrhythmia, IV calcium should be administered to reverse respiratory depression, hypotension, and cardiac arrhythmia. Emergent dialysis should be considered to correct life-threatening hypermagnesemia in the presence of impaired renal function.

Hypomagnesemia

Magnesium is a major inorganic cation in the body, of which only 1–2% is present in the extracellular space.

Hypomagnesemia is defined as a plasma serum concentration of magnesium less than 1.5 mg/dL. However, magnesium levels that are persistently less than 1.8 mg/dL indicate depletion of total body magnesium. The prevalence of hypomagnesemia in hospitalized cancer patients is about 20%.

Causes:

- Low oral intake, impairment of renal reabsorption, prolonged IV feeding, chronic alcoholism, intestinal malabsorption, and diarrhea.
- The renal toxicity of chemotherapy (e.g., platinum-based drugs, cyclophosphamide, ifosfamide) or anti-infective medications (e.g., amphotericin, aminoglycosides) will also cause hypomagnesemia. Platinum agents cause morphologically evident nephrotoxicity that may result in long-term or even permanent damage to renal functions. Hypomagnesemia occurs in approximately 90% of patients treated with cisplatin [8], and 10% of the hypomagnesemic patients have symptoms of muscle weakness, tremors, and dizziness. Hypomagnesemia may persist long after cessation of cisplatin therapy.
- Anti-EGFR targeted therapy (cetuximab, panitumumab, and anti-EGFR small molecular inhibitors such as gefitinib) reduces renal magnesium reabsorption through a reversible effect of epidermal growth factor receptor (EGFR) inhibition in the renal distal convoluted tubule without inflicting extensive cell or organ injury [9].

Symptoms Magnesium is needed for a wide variety of enzymatic reactions, including those involving ATP and nucleic acid metabolism. Magnesium is also directly involved in the regulation of calcium and potassium metabolism. The clinical manifestations of hypomagnesemia may be nonspecific and include anorexia, nausea, vomiting, lethargy, dizziness, muscle weakness, tremor, muscle fasciculation, tetany, and tonic-clonic seizures.

Diagnosis Hypomagnesemia is often associated with other electrolyte abnormalities, such as hypokalemia and hypocalcemia [10]. Concurrent measurement of other electrolytes, such as calcium, phosphate, and potassium, should be considered. Significant hypomagnesemia is associated with EKG changes (see Fig. 29.3). According to CTCAE version 4, hypomagnesemia is Grade 1 when magnesium is below normal to ≥0.5 mM; Grade 2, <0.5–0.4 mM; Grade 3, <0.4–0.3 mM; and Grade 4, <0.3 mM with life-threatening consequences.

Management Magnesium replacement is indicated in cancer patients when serum magnesium is repeatedly below normal. Oral replacement is preferred over parenteral when feasible. However, diarrhea may be a dose-limiting side effect. When IV replacement is required, the usual practice is to replace half of the estimated dose over 1 day and the remaining half over the next 3–4 days. Hypomagnesemia induced by anti-EGFR-therapy is reversible.

Hypercalcemia

The incidence of hypercalcemia in cancer patients is about 1% [11].

Causes:

- Hypercalcemia of malignancy accounts for more than 90% of hypercalcemia cases:
  1. Parathyroid hormone-related protein (PTHrP)-mediated hypercalcemia [12, 13] is a paraneoplastic syndrome associated with a short survival. PTHrP causes hypercalcemia by binding to the parathyroid hormone (PTH) receptor and activating the expression of an osteoblast-specific cell surface protein, RANK ligand (RANKL). Interaction between RANKL and the RANK receptor on the osteoclast precursor causes increased osteoclast differentiation, bone resorption, and hypercalcemia. PTHrP production is found commonly in squamous cell carcinoma, breast, neuroendocrine, renal, and prostate cancers, as well as melanoma.
  2. Other tumor-secreted humoral factors, such as interleukin-1 and -6, prostaglandins and tumor necrosis factor, may contribute to hypercalcemia.
  3. In multiple myeloma, increased expression of RANKL causing localized osteoclast proliferation appears to be the most important cause [13].
  4. Lymphomas commonly express 1α-hydroxylase, the enzyme that converts 25-hydroxy vitamin D3 to 1,25-dihydroxy vitamin D3 (calcitriol), leading to increased gastrointestinal absorption of calcium [14].
- Primary hyperparathyroidism should be considered in the differential diagnosis of hypercalcemia. No cancer treatment has been identified as a cause of hypercalcemia, except that low-dose (2–7.5 Gy) external-beam irradiation of the head and neck area increases the incidence of primary hyperparathyroidism by 2.5- to 3-fold many years after irradiation of the neck (29–47 years) [15]. Primary hyperparathyroidism may also develop in multiple endocrine neoplasia (MEN), especially type 1.

Symptoms Patients with mild hypercalcemia (calcium level <12 mg/dL) usually have no symptoms, whereas those with moderate or severe hypercalcemia are frequently symp-

tomatic. Central nervous system symptoms are lethargy, ataxia, stupor, coma, mental status changes, and psychosis. Gastrointestinal tract symptoms are anorexia, nausea, constipation, ileus, dyspepsia, and pancreatitis. Renal signs are polyuria, nephrolithiasis, and nephrocalcinosis. Cardiovascular manifestations can be a short QT interval, ST segment depression, sinus arrest, and atrioventricular block (see Fig. 29.3). Musculoskeletal symptoms are myalgia, arthralgia, and weakness. Severe hypercalcemia (>13 mg/dL) frequently causes depression of cerebral function or coma.

Diagnosis Serum calcium levels should be interpreted in the context of protein binding (corrected calcium level = [0.8 × (normal albumin level - patient's albumin level)] + serum calcium level). Measurement of the ionized calcium can confirm hypercalcemia. Laboratory studies of the following help diagnose the etiology of hypercalcemia: intact PTH, PTH-related protein, 25-hydroxy vitamin D_3, and 1,25-dihydroxy vitamin D_3. The combination of hypercalcemia and an elevated PTH level combined with increased urinary calcium excretion provides reasonable evidence for primary hyperparathyroidism. Suppression of the PTH below the normal range is found in PTHrP or calcitriol-mediated hypercalcemia, which can be diagnosed by measuring 25-hydroxy vitamin D3 and 1,25-dihydroxy vitamin D3.

PTHrP-mediated hypercalcemia is characterized by a suppressed PTH level and a low or normal calcitriol level. This contrasts with the finding of elevated PTH and calcitriol levels in primary hyperparathyroidism. The characteristic clinical features of hypercalcemia in lymphoma include a suppressed serum PTH, a normal or slightly increased phosphate level due to suppression of PTH, hypercalciuria, absence of bone metastasis, and an elevated serum calcitriol level [14].

Management:

- The initial and first-line treatment of hypercalcemia is hydration by infusion of normal saline at rates between 100 and 300 mL/h. Hydration alone can lower the serum calcium by 10% or more over 6–12 hours. In patients with overall fluid overload, use of a loop diuretic would be helpful.
- Calcium-containing medications and thiazide diuretics (which inhibit renal tubular excretion of calcium) should be discontinued.
- Bisphosphonates inhibit bone resorption by osteoclasts, and their peak impact on hypercalcemia is usually seen after a couple of days. Zoledronate (4–6 mg IV over 30 minutes) [16] is more widely used than pamidronate (60–90 mg IV over 4–24 hours) because of its higher potency and efficacy [17].
- Second-line agents include calcitonin (salmon calcitonin 4 IU/kg subcutaneously every 12 hours). Calcitonin has a rapid onset of action, but its effectiveness may decrease within 2–3 days.
- Glucocorticoids (40–60 mg/d prednisone equivalent) may be used in hypercalcemia associated with myeloma and lymphoma.
- Denosumab (anti-RANKL antibody) is a new drug for hypercalcemia of malignancy [18].
- Primary hyperparathyroidism can be cured via parathyroidectomy. Removal of adenoma is usually curative, but in the context of MEN1, the surgical procedure of choice is three-and-a-half-gland parathyroidectomy [19].

Hypocalcemia

Hypocalcemia is a common complication of chemotherapy [20].

Causes:

- Nephrotoxicity of platinum compounds: Hypocalcemia has been reported in 6–20% of cisplatin-treated and 16–31% of carboplatin-treated patients. Hypomagnesemia may decrease secretion of PTH and reduce its calcium-mobilizing effects. Hypomagnesemia also inhibits the formation of 1,25-dihydroxy vitamin D_3. Platinum compounds may inhibit the mitochondrial function in the kidneys and thereby inhibit conversion of 25-hydroxy vitamin D_3 to 1,25-dihydroxy vitamin D_3.
- Plicamycin (mithramycin) and dactinomycin are two infrequently used antineoplastic agents that are known to cause hypocalcemia.
- Surgical procedures in the neck that sacrificed or damaged the parathyroid glands (e.g., total laryngectomy, total thyroidectomy) can cause primary hypoparathyroidism, leading to hypocalcemia.
- Vitamin D deficiency causes rickets and osteomalacia along with hypocalcemia.
- Tumor lysis syndrome.

Symptoms Hypocalcemia can be asymptomatic if it is mild. Life-threatening problems such as seizures, cardiac dysrhythmias, and laryngospasm can occur if hypocalcemia is severe. Acute hypocalcemia is characterized by neuromuscular irritability. Acute symptoms are muscle weakness, paresthesia, spasm, tetany, hyperreflexia, Chvostek sign, Trousseau sign, seizure, bronchospasm, laryngeal spasm, and respiratory failure. Cardiovascular presentations are bradycardia, hypotension, QT-interval prolongation (see Fig. 29.3), congestive heart failure, and cardiac arrest. Chronic hypocalcemia with hypoparathyroidism causes extrapyramidal disorders and cataracts, as well as skin and hair changes.

Diagnosis Measuring ionized calcium can exclude pseudohypocalcemia owing to low albumin and serum protein levels. In most cancer patients, the etiology of hypocalcemia is obvious. The major causes of hypocalcemia are hypoparathyroidism, hypomagnesemia, and chemotherapy toxicity. If the cause of hypocalcemia is not clear, laboratory analysis of intact PTH, magnesium, phosphate, 25-hydroxy vitamin D3, 1,25-dihydroxy vitamin D3, creatinine and 24-hour urinary calcium levels is helpful.

Management:
- Severe hypocalcemia is treated parenterally with IV calcium chloride (0.5–1.0 g) or gluconate (1–2 g) over 5–10 minutes.
- Hypomagnesemia is a common cause of hypocalcemia. Concurrent hypomagnesemia should be treated with IV magnesium sulfate followed by oral replacement.
- Chronic hypocalcemia is treated with oral calcium preparations (e.g., gluconate, carbonate) containing 1–2 g of elemental calcium per day.
- Patients with hypoparathyroidism often require life-long supplementation of calcium and vitamin D. Vitamin D supplements can be given in 1-hydroxylated form or as calcitriol.
- Recombinant $PTH_{1–34}$ (teriparatide) is now approved for the treatment of osteoporosis. Its use in hypoparathyroidism remains to be studied.
- For hypocalcemia secondary to hyperphosphatemia, hyperphosphatemia often requires correction first. See below for management of hyperphosphatemia.

Hyperphosphatemia

In the absence of renal failure, the fasting serum phosphate level is determined primarily according to the renal tubular reabsorption rate.

Causes:
- A massive amount of phosphate can be released into the extracellular fluid via extensive cellular breakdown (e.g., tumor lysis syndrome, rhabdomyolysis, and hemolysis).
- Translocation of phosphate from cells in response to metabolic or respiratory alkalosis can lead to acute hyperphosphatemia.
- Chronic hyperphosphatemia is present in patients with hypoparathyroidism on long-term treatment with oral calcium and vitamin D.
- Excess phosphate intake (e.g., phosphate-containing laxatives), especially in the presence of renal insufficiency.

Symptoms The clinical manifestations of acute hyperphosphatemia are similar to those of associated hypocalcemia. Paresthesia, muscle cramps, tetany, and QT-interval prolongation may be induced directly by severe hyperphosphatemia. Chronic hyperphosphatemia, especially associated with hypercalcemia, may lead to diffuse visceral deposition of calcium phosphate. Deposition of calcium phosphate in the kidneys may lead to renal failure.

Diagnosis In patients with hyperglobulinemia, pseudohyperphosphatemia must be excluded with a specimen that is free of protein (removed via precipitation with sulfosalicylic acid). In those with hyperphosphatemia, renal function must be assessed. In addition, measurement of lactic dehydrogenase, uric acid, potassium, and calcium levels is necessary to diagnose and manage hyperphosphatemia due to extensive cellular lysis.

Management:
- In patients with normal renal function, infusion of isotonic saline increases phosphate excretion.
- Administration of dextrose and insulin drives phosphate into cells, temporarily lowering the serum phosphate level.
- When hyperphosphatemia is life-threatening, hemodialysis or peritoneal analysis should be considered.
- Blocking phosphorus absorption in the gastrointestinal tract:
  1. Aluminum hydroxide
  2. Calcium-based phosphate binders (e.g., calcium acetate)
  3. Nonabsorbable phosphate binders that are aluminum- and calcium-free (sevelamer 800–1600 mg with each meal)

Hypophosphatemia

Hypophosphatemia is found in about 2–3% of all hospitalized patients and about 30% of cancer patients.

Causes:
- Relative nutritional deficiency:
  1. Hypophosphatemia in malnourished patients (especially alcoholics) is due to a combination of magnesium deficiency, vitamin D deficiency, and malabsorption. Acute hypophosphatemia may occur in hospitalized patients with serious illnesses and preexisting phosphate depletion.
  2. Refeeding with high-calorie contents in severely malnourished patients.

3. Rapid cancer proliferation may cause hypophosphatemia (e.g., Burkitt's lymphoma).
4. Rapid normal cell proliferation, as with the use of granulocyte colony-stimulating factors, hematopoietic reconstitution after stem cell transplantation, or stem cell harvesting in preparation for transplantation.

- Renal wasting of phosphorus and calcium:
  1. Tumor-induced osteomalacia is a rare paraneoplastic syndrome characterized by hypophosphatemia, excessive urinary phosphate loss, reduced 1,25-dihydroxy vitamin D concentrations, and osteomalacia. Fibroblast growth factor-23 may be the humoral mediator of this paraneoplastic syndrome [21]. Tumors that produce this clinical syndrome include mesenchymal tumors (osteoblastomas, giant cell osteosarcomas, hemangiopericytomas, hemangiomas, nonossifying fibromas) [22] and, rarely, malignant tumors such as prostate or lung cancer.
  2. Intrinsic renal tubular defect in phosphate reabsorption, or acquired renal tubular defect (e.g., after ifosfamide [23], cisplatin [24], and estramustine [25]).
- Transcellular shift of phosphate (e.g., respiratory alkalosis, IV glucose administration, hyperalimentation, gram-negative sepsis, or insulin therapy).
- Elevated PTH (primary hyperparathyroidism) or PTHrP (hypercalcemia of malignancy).
- Accelerated bone formation (e.g., extensive blastic bone metastasis in prostate cancer, hungry bone syndrome after resection of parathyroid adenomas).
- Loss of liver function: The liver also plays a significant role in phosphate homeostasis. Serum phosphate decreases after right or extended right hepatic lobectomy and in hepatocellular carcinoma complicating liver cirrhosis.
- Consumption of aluminum-containing medications/antacids.

Symptoms Acute severe hypophosphatemia may lead to general neurologic findings such as lethargy, confusion, disorientation, hallucinations, and focal neurologic findings such as dysarthria, dysphagia, oculomotor palsy, anisocoria, nystagmus, ataxia, cerebellar tremor, ballismus, hyporeflexia, distal sensory deficits, paresthesia, and hyperesthesia. Severe neurologic symptoms, such as muscle paralysis, seizure, and coma, are observed only when the serum phosphate level is <0.8 mg/dL. In severe hypophosphatemia, reversible left ventricular dysfunction can occur.

Muscle weakness is the most common complaint. Bone pain is another prominent complaint of phosphate-depleted patients. Prolonged hypophosphatemia leads to rickets. Osteomalacia, a condition characterized by unmineralized bone matrix, should be considered in osteopenic patients with bone pain and proximal myopathy. Waddling gait, bone tenderness, pseudo-fractures, and fractures can occur in patients with chronic hypophosphatemia. Osteomalacia and moderate to severe proximal myopathy are also characteristics of tumor-induced osteomalacia [26].

Diagnosis Measurement of renal function and potassium, magnesium, ionized calcium, vitamin D metabolites, and PTH level is helpful in the initial evaluation of the cause of hypophosphatemia. If urinary loss of phosphate is suspected, urine should be collected to measure the renal phosphate threshold/glomerular filtration rate to confirm phosphaturia.

Management:

- Significant hypophosphatemia (phosphate level less than 2 mg/dL), especially in the context of underlying phosphate depletion, should be corrected promptly.
- Phosphate can be safely administered IV at an initial dose of 0.2–0.8 mmol/kg over 6 hours (i.e., 10–50 mmol over 6 hours). Higher doses (1.5–3.0 mmol/kg over 12 hours) should be reserved for patients with phosphate levels less than 1.5 mg/dL and normal renal function.
- Mild hypophosphatemia can be treated with oral phosphate in divided doses of 750–2000 mg/day.
- For tumor-induced osteomalacia, oral or IV supplementation of phosphate combined with vitamin D therapy is generally effective for eradicating or improving clinical symptoms. Complete surgical removal of the tumor is generally curative.

Hyperglycemia

Diabetes mellitus type 2 (DM2) is a common disease, and a large number of cancer patients have co-existing DM2. Extensive epidemiologic data suggest an important role of DM2 in carcinogenesis [27–32] and cancer survival [33], and DM2 is associated with an elevated risk of pancreatic, liver, colon, gastric, breast, and endometrial cancer [27–32].

Causes:

- The administration of glucocorticoids (e.g., for antineoplastic therapy in combination regimens, for edema of brain metastasis, for prevention of transplant rejection, for graft-versus-host disease in BMT, and for nausea/vomiting) is probably the most common cause of drug-induced diabetes in cancer patients.
- Treatment with streptozocin [34] or L-asparaginase [35] may result in insulin-deficient diabetes mellitus.
- Diabetes mellitus may also develop as a consequence of serious pancreatitis secondary to treatment with L-asparaginase.
- Interleukin-2 and interferons may cause toxicity to pancreatic β cells and lead to insulin-dependent diabetes [36].

Immune checkpoint inhibitors may cause acute development of type I diabetes and precipitate the serious complication of diabetic ketoacidosis.

- Some targeted therapy antineoplastic agents interfere with the insulin signaling pathway and can cause hyperglycemia. PI3K inhibitors (alpelisib, copanlisib, duvelisib, and idelalisib) and mTOR inhibitors (e.g., rapamycin (sirolimus), everolimus, and temsirolimus) are associated with a high incidence of hyperglycemia [37, 38]. Some tyrosine kinase inhibitors (TKIs) (e.g., niltinib and sunitinib) are associated with hyperglycemia, but some TKIs (e.g., imatinib and pazopanib) may be associated either with hyperglycemia or with hypoglycemia [38].
- Tacrolimus, an immunosuppressive agent used to prevent graft-versus-host disease in bone marrow stem cell transplantation, also increases the incidence of diabetes, perhaps by damaging pancreatic β cells [39]. Patients who received allogenic stem cell transplantation are likely to be receiving both glucocorticoids, cyclosporine A and tacrolimus, and are particularly at risk for developing diabetes mellitus [40].

Symptoms Most patients with significant hyperglycemia have symptoms of polydipsia, polyuria, and polyphagia. Dehydration of the lenses owing to hyperglycemia leads to blurry vision. Patients with hyperosmolar nonketotic coma experience mental status changes, hypotension, and severe dehydration. Nausea, vomiting, and abdominal pain are present in almost half of patients with diabetic ketoacidosis. Tachypnea with Kussmaul respiration, tachycardia, hypotension, orthostatic blood pressure changes, acetone breaths, and severe signs of dehydration can be present in patients with diabetic ketoacidosis.

Diagnosis A random plasma glucose >200 mg/dL or a fasting plasma glucose >126 mg/dL on more than one occasion can indicate diabetes mellitus. Abnormal glucose may require further diagnostic evaluation with a glucose tolerance test or mixed meal tolerance test or glycosylated hemoglobin (hemoglobin A1C).

Diabetic ketoacidosis is diagnosed according to the triad of metabolic acidosis, hyperglycemia, and the presence of ketone bodies in the urine or blood. Arterial blood gas testing will demonstrate acidemia and respiratory compensation for metabolic acidosis by hyperventilation. Also, the anion gap will be elevated, and serum ketone testing will be positive. A urine dipstick test for ketones can provide timely information for a quick bedside diagnosis. Absence of ketones from the urine practically excludes diabetic ketoacidosis. Leukocytosis may be associated with ketosis, but an infection must be considered as a precipitating factor for diabetic ketoacidosis. The serum creatinine level can be falsely elevated because of ketosis. Potassium, phosphate, and magnesium abnormalities result from transcellular shifts caused by acidosis.

In hyperosmolar hyperglycemic nonketotic coma, the plasma glucose level may be >800 mg/dL and the serum osmolality may be >100 mOsm above normal. Mild ketosis may be present because of starvation, but ketoacidosis is absent. In severe cases, when volume depletion compromises tissue perfusion, lactic acidosis will develop.

In immunocompromised cancer patients in particular, sepsis must be ruled out as the precipitating event for diabetic ketoacidosis or hyperosmolar hyperglycemic coma.

Management:

- In general, insulin will be needed in patients who are insulin deficient.
- Diabetic ketoacidosis is decompensated catabolism triggered by a relative or absolute deficiency in insulin secretion.
- Treatment of diabetic ketoacidosis or hyperosmolar hyperglycemic coma:
  1. Hydration with IV crystalloid fluid.
  2. Regular insulin, which usually is given as an IV bolus of 0.1 U/kg, followed by a maintenance IV infusion of 0.1 U/kg/hour. The amount of insulin required for treatment of hyperosmolar hyperglycemic coma may be less than that required for diabetic ketoacidosis.
  3. Correction of electrolyte abnormalities, but beware of transcellular shift of electrolytes related to blood pH and the effect of insulin.
  4. Identification of the precipitating factors (particularly important to rule out sepsis).

Hypoglycemia

Glucagon and epinephrine immediately stimulate hepatic glycogenolysis followed by gluconeogenesis and are the two major counterregulatory hormones in response to hypoglycemia. Other counterregulatory hormones are norepinephrine, cortisol, and growth hormone, but their effects are delayed.

Causes:

- Cancer-related malnutrition, fat and muscle wasting, cirrhosis, and extensive liver metastases may impair glycogenolysis and gluconeogenesis.
- Adrenal insufficiency is associated with hypoglycemia; refer to the section on adrenal crisis below for detailed discussion.
- For diabetic cancer patients receiving sulfonylurea or insulin, the most common cause of hypoglycemia may be delayed or decreased food intake. The kidneys contribute to overall gluconeogenesis during hypoglycemia stress in

about one third of cases and are important to extrahepatic degradation of insulin. Moreover, a number of oral hypoglycemic drugs are excreted by the kidneys. Therefore, decline in renal function often leads to hypoglycemic episodes in diabetic patients.

- Tumor-induced hypoglycemia is an uncommon but challenging cause of morbidity for cancer patients. Three different clinical syndromes have been identified: (1) secretion of insulin by islet cell malignancy; (2) insufficient gluconeogenesis due to near complete replacement of hepatic parenchyma by tumor; and (3) secretion of insulin-like growth factor II (IGF2), which activates the insulin receptor and causes hypoglycemia [41–43] by tumors (e.g., fibrosarcomas, hemangiopericytomas, and hepatomas).
- Excessive glucose consumption by large tumors also may cause hypoglycemia. Hypoglycemia may also occur in patients with lactic acidosis in the context of end-stage leukemia or lymphoma [44].

Symptoms A pattern of hypoglycemia symptoms progresses as the availability of glucose to the brain decreases. At a plasma glucose level of about 70 mg/dL, brain glucose uptake can be reduced and counterregulatory hormone responses are triggered. At <60 mg/dL, autonomic symptoms, such as hunger, anxiety, palpitations, sweating, and nausea, become evident. When glucose <50 mg/dL, neuroglycopenic symptoms of blurry vision, slurred speech, inability to concentrate, and confusion appear. When glucose <40 mg/dL, the patient may become drowsy, confused, or combative. A prolonged decrease below 30 mg/dL can cause seizures, permanent neurologic damage, and death.

Diagnosis Hypoglycemia is diagnosed by blood chemistry, but rapid bedside measurement of blood glucose should be expeditiously performed in the evaluation of all ED patients with altered mental status. The timing of symptoms relative to a fasting or postprandial state or to anti-diabetic medications can distinguish among various causes of hypoglycemia.

The most common presentation for paraneoplastic syndromes of hypoglycemia is fasting hypoglycemia, and patients are most likely to develop symptoms during normal periods of fasting, particularly during nocturnal hours. Simultaneous measurement of fasting plasma glucose, insulin, proinsulin, C-peptide, IGF1, and IGF2 during a period of hypoglycemia is the most important diagnostic tool for separating the first clinical type (insulin production) from the second (replacement of liver by tumor) and third (IGF2) types. Proper diagnostic evaluation of cancer patients with fasting hypoglycemia usually will need a 72-hour fast in the hospital with endocrinology consultation.

Management:

- For mild hypoglycemia (glucose level of 50–60 mg/dL), 15 g of simple carbohydrates, such as 4 oz of unsweetened fruit juice or a non-diet soft drink, is sufficient.
- For more severe hypoglycemia without loss of consciousness, 15–20 g of simple carbohydrates should be ingested quickly followed by 15–20 g of a complex carbohydrate, such as crackers or bread.
- For severe hypoglycemia with change in mental status, glucagon (1–2 mg subcutaneously or IV) or glucose (50 mL of 50% dextrose in water IV) should be given promptly.
- The most effective therapeutic approach for non-islet cell tumor-induced hypoglycemia is to resect or debulk the tumor. If unresectable, reducing the tumor bulk via external beam irradiation, intra-arterial chemoembolization, or percutaneous alcohol injection may be attempted.
- Counterregulatory hormones such as glucocorticoids (20–40 mg prednisone equivalents per day) and glucagon (1–2 mg IV or IM) may be administered to raise the blood glucose level. Glucagon infusion (0.5–2 mg/h) to stimulate hepatic gluconeogenesis is an effective therapy for patients with insulin-producing tumors or those with IGF2-mediated hypoglycemia [45].
- A continuous IV infusion of 5–20% dextrose may be required to maintain normal blood glucose in some patients.
- Diazoxide (3–8 mg/kg/d in 2–3 divided doses) has been used successfully to inhibit insulin secretion, but it causes fluid retention, thereby limiting its usefulness at effective doses.
- Treatment of postprandial hypoglycemia is primarily dietary. The diet should have a low carbohydrate content. α-Glucosidase inhibitors (acarbose or miglitol) may be helpful.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) consists of severe hyperphosphatemia, hyperkalemia, hyperuricemia, azotemia, hypocalcemia, and metabolic acidosis (out of proportion to renal insufficiency) due to the massive release of cell contents and degradation products of dead tumor cells into the bloodstream [46].

Causes:
Factors associated with increased risk of TLS include the following:

- Type of malignancy (e.g., acute lymphocytic leukemia, acute myeloid leukemia with WBC >75,000/μL, Burkitt's

lymphoma). TLS can also occur in patients with nonhematologic malignancies, including small cell carcinomas, non-small cell lung cancer, breast cancer, and ovarian cancer.
- Responsiveness to therapy.
- Rapid malignant cell turnover.
- Large tumor burden [47]; pretreatment serum lactate dehydrogenase levels, which tend to correlate with tumor bulk in lymphoma or lymphocytic leukemia may predict the risk of tumor lysis syndrome.
- Preexisting renal insufficiency.
- Acute renal failure shortly after antineoplastic treatment.

Symptoms The symptoms of TLS are nonspecific. Common symptoms include nausea, vomiting, cloudy urine, weakness, fatigue, and arthralgia. Other signs and symptoms related to metabolic and electrolyte abnormalities include neuromuscular irritability, seizures, muscle weakness, and arrhythmia. Arrhythmia may cause sudden death in patients with TLS [48]. Precipitation of uric acid in the renal tubules may lead to nephropathy and acute renal failure [49]. The acute cause of death in TLS is arrhythmia secondary to severe electrolyte abnormalities (especially hyperkalemia) and renal failure. Early recognition of metabolic abnormalities and prompt treatment can avoid fatal outcomes.

Diagnosis TLS can occur spontaneously, but it usually occurs within 72 hours after chemotherapy in patients with leukemia and lymphoma, but new therapeutic regimens may alter the timing of onset. The diagnosis of TLS requires a high level of suspicion because there are few signs or symptoms in the early stage. Routine uric acid and electrolyte screening (including measurement of calcium and phosphorus levels) is indicated in patients with high tumor bulk or hematologic malignancies. The diagnosis of TLS may be based on the Cairo-Bishop definition [47, 50].

Management:
- Once diagnosed, patients with severe TLS should have continuous monitoring of hemodynamic and electrocardiographic parameters in intensive care.
- Management of hyperuricemia:
  1. Allopurinol (up to 900 mg/day)
  2. Rasburicase (150–200 μg/kg IV daily or one-time dosing with a rescue dose as needed) is a recombinant urate oxidase that converts uric acid to allantoin [51]
  3. IV fluid hydration may be coupled with diuresis using loop diuretics (e.g., furosemide, 20–200 mg IV every 4–6 hours) and acetazolamide (250–500 mg IV daily).
  4. Urinary alkalinization by sodium bicarbonate or acetate IV infusion to increase the solubility of urate in urine should only be considered in cases of severe hyperuricemia when rasburicase is not available.
- Frequent electrolyte measurements (every 4–6 hours) may be required. See the sections above about management of hyperkalemia, hypocalcemia, and hyperphosphatemia.
- Prompt dialysis should be instituted with continued monitoring until biochemical abnormalities resolve. Indications for dialysis in patients with TLS include the following:
  1. Symptomatic hypocalcemia and a serum phosphorus level greater than 3.3 mmol/L (>10.2 mg/dL)
  2. Severe azotemia and renal failure (creatinine >10 mg/dL)
  3. Persistent hyperkalemia (>6 mEq/L)
  4. Severe hyperuricemia (> 10 mg/dL)
  5. Oliguria or anuria despite diuretic use
  6. Refractory academia
  7. Volume overload

Endocrine Emergencies

Cushing Syndrome

Inappropriate secretion of ACTH, although uncommon, is an important cause of morbidity and mortality in certain types of malignancies. There are at least two different mechanisms: ectopic ACTH production or ectopic production of CRH, the hypothalamic peptide that normally stimulates ACTH synthesis and release.

Causes:
- The most common cause of ectopic ACTH production is the expression of proopiomelanocortin (POMC) by a tumor, producing melanocyte-stimulating hormone and ACTH. The most common tumor associated with ACTH production is small cell lung cancer (SCLC), although pulmonary carcinoid, medullary thyroid carcinoma, islet cell malignancy, pheochromocytoma, and occasional ganglioneuromas can also produce this hormone.
- The second cause of excessive ACTH production is tumor production of CRH [52]. Ectopic production of this peptide causes a clinical syndrome characterized by pituitary corticotroph hyperplasia leading to adrenal cortical hyperplasia and Cushing syndrome. Identification of excessive CRH production requires that the clinician consider this possibility and measure CRH in blood. Neoplasms that can produce CRH include medullary thyroid carcinoma, paragangliomas, prostate cancer, and islet cell neoplasms.

Symptoms Patients with ectopic ACTH syndrome may present with clinical features of Cushing syndrome—easy bruising, centripetal obesity, muscle wasting, hypertension, diabetes, and metabolic alkalosis predominate. Alternatively,

patients with rapidly growing SCLC may present with a clinical syndrome characterized by wasting, muscle atrophy, profound hypokalemic metabolic alkalosis, and hypertension without the other clinical signs of Cushing syndrome.

Diagnosis The hallmark of ectopic ACTH syndrome is the finding of an elevated plasma ACTH concentration. However, in the differential diagnosis of hypercortisolism with an elevated plasma ACTH concentration, the clinician should consider the possibility of an ACTH-producing pituitary tumor [53]. Differentiation between pituitary ACTH production and ectopic tumor production of ACTH or ectopic CRH production should be performed by a consultant endocrinologist, and therefore will not be discussed in detail here. In brief, the diagnostic evaluation starts with confirmation of hypercortisolism and measuring plasma ACTH, followed by dynamic testing, and may involve MRI of pituitary or petrosal venous sinus sampling.

Management:

- Medical management to inhibit cortisol production:
  1. Metyrapone (1–4 g/d orally).
  2. Aminoglutethimide (250 mg orally four times per day with upward titration).
  3. Ketoconazole (200–400 mg twice a day orally) [54].
  4. Etomidate rapidly inhibits cortisol synthesis at subhypnotic doses [55]. It may be titrated from 0.3 to 4 mg/kg/h IV to normalize serum cortisol in some selected patients.
- Surgical removal or treatment of the tumor with chemotherapeutic agents is the primary therapy for an ACTH- or CRH-producing tumor.
- Patients with rapidly progressive small cell lung cancer and ectopic ACTH syndrome have a unique challenge due to the need to initiate chemotherapy quickly. High susceptibility to opportunistic infections after initiation of chemotherapy will often lead to death or serious morbidity [56]. Laparoscopic adrenalectomy, following normalization of electrolyte abnormalities and hypertension, may rapidly treat hypercortisolism to decrease the risk of infectious complication after chemotherapy.
- Replacement glucocorticoid therapy will be needed after adrenalectomy or during pharmacologic inhibition of cortisol production.
- Prophylactic therapy for opportunistic infections caused by *Pneumocystis carinii* or fungi should be considered if chemotherapy is initiated shortly after normalization of the serum cortisol.

Adrenal Crisis

Cancer patients are at increased risk for adrenal insufficiency.

Causes:

Central Adrenal Insufficiency:

- Radiotherapy is a common cause of insidious development of hypothalamic dysfunction; hormonal deficiency can manifest years after radiation. In general, the rapidity of onset and severity of dysfunction depend on the total dose of radiation and the rate of delivery. The somatotropic axis is the most susceptible while the thyrotropic is the least susceptible [57–60].
- High-dose glucocorticoids may suppress the hypothalamic-pituitary-corticotropic axis. In cancer patients who have recently discontinued glucocorticoid therapy, acute stress (usually from infection/sepsis) may precipitate an adrenal crisis.
- Acute central adrenal insufficiency may occur in cancer patients in the following settings:
  1. Pituitary apoplexy
  2. Autoimmune hypophysitis after starting cancer immunotherapy (especially with immune checkpoint inhibitors, i.e., anti-CTLA4, anti-PD1, or anti-PD-L1 antibodies)
- Metastasis to the hypothalamic region or the pituitary gland is uncommon [61].
- Benign tumors such as pituitary tumors and craniopharyngiomas frequently affect this anatomic region and cause endocrine dysfunction.

Primary Adrenal Insufficiency:

- About 20–30% of patients with bilateral adrenal metastasis will have adrenal insufficiency [62], which occurs when more than 80% of adrenal tissue is destroyed or replaced by metastatic cancer [63].
- Bilateral infectious adrenalitis: Many cancer patients may be immunocompromised. In immunocompromised patients with hematological malignancies or stem cell transplantation, infection of the adrenal glands by cytomegalovirus, mycobacteria, or fungi may lead to adrenal insufficiency.
- Bilateral adrenal hemorrhage (e.g., in coagulopathy and thrombocytopenia).
- Bilateral adrenalectomy (e.g., radical nephrectomy and contralateral adrenalectomy for renal cell carcinoma and bilateral adrenal metastasis).
- Autoimmune adrenalitis (e.g., immune checkpoint inhibitors).
- Drugs that are known to inhibit glucocorticoid synthesis: etomidate [62], ketoconazole, aminoglutethimide, metyrapone, megestrol, and mitotane. At high doses, fluconazole and itraconazole may also inhibit the cytochrome P450-dependent enzymes in glucocorticoid synthesis.

Symptoms The symptoms of adrenal insufficiency include weakness, fatigue, nausea, vomiting, and weight loss. In

patients with chronic primary adrenal failure, hyperpigmentation may occur. Acute adrenal crisis involves hypoglycemia and hypotension. The cachexia and weakness seen in adrenal insufficiency can mimic cancer cachexia observed among end-stage cancer patients. Electrolyte abnormalities due to adrenal insufficiency are difficult to distinguish from poor intake, malnutrition, side effects of chemotherapeutic agents, or paraneoplastic syndromes. Both pituitary apoplexy and hypophysitis may be associated with headache.

Diagnosis The medication history should be reviewed for recent glucocorticoid exposure and medications that may inhibit steroid synthesis. Screening tests include basal 8:00 a.m. plasma cortisol measurement, dynamic testing with 1 μg of cosyntropin (synthetic $ACTH_{1–24}$) or metyrapone (30 mg/kg given orally overnight), and insulin tolerance testing (insulin-induced hypoglycemia).

Without other evidence of metastatic disease elsewhere, whether an adrenal mass is actually a metastatic tumor is critical information in determining the appropriate antineoplastic therapy. In addition to hormonal evaluation, functional scintigraphy using ^{131}I-6-iodomethyl-19-*nor*-cholesterol (NP-59), CT, and MRI may aid in the diagnosis of a unilateral adrenal mass greater than 2 cm [64, 65]. In immunocompromised patients, the possibility of infection of both adrenal glands with cytomegalovirus, mycobacteria, or fungi should be investigated. A high degree of suspicion for hypopituitarism is recommended for patients given ipilimumab, or perhaps other drugs with similar mechanisms of action.

Management If a cancer patient presents to an E with hemodynamic instability, physicians may have insufficient time to wait for the results of serum cortisol measurement or other tests to evaluate adrenal insufficiency. Under such circumstances, empiric treatment with a stress dose of hydrocortisone should be considered based on risk assessment.

- In the event of circulatory instability, sepsis, emergency surgery, or other major complications, stress dosages of parenteral glucocorticoid should be given (e.g., hydrocortisone succinate 100 mg IV every 8 hours).
- Fludrocortisone (0.05–0.20 mg/day) for mineralocorticoid replacement.
- Treat hypotension with IV normal saline or other crystalloid fluid.
- Treat hypoglycemia immediately if symptomatic. Dextrose 50% in water 50–100 mL IV, followed by D5W IV. If IV access is not quickly available, glucagon (2 mg) may be given subcutaneously or intramuscularly, but the effect may be delayed by about 10–20 minutes.
- If and when the patient is clinically stable, arrangement should be made for endocrinology consultation and the ACTH stimulation test.

Hyperthyroidism

Thyrotoxicosis is a common disease with a prevalence of 20–25 per 100,000 in the general population and a female:male ratio of 5:1.

Causes:

- Graves disease, toxic multinodular goiters, and solitary toxic nodules are the three forms of primary hyperthyroidism that account for most cases of hyperthyroidism in the general population. The risk of Graves disease after radiotherapy for Hodgkin disease is estimated to be at least 7.2 times that in the general population [66]. Immune checkpoint inhibitors may induce Graves disease in rare occasions.
- Large quantities of iodide are present in many drugs (e.g., approximately 9 mg of iodine following a daily amiodarone dose of 300 mg), antiseptics (e.g., povidone-iodine), and contrast media used in radiology. Iodine-induced hyperthyroidism usually occurs in patients with underlying thyroid diseases.
- Autoimmune thyroiditis may be precipitated by bioimmunotherapy for cancer with cytokines or immune checkpoint inhibitors. In addition to being a source of excess iodide described above, amiodarone may induce thyroiditis. Transient hyperthyroidism is usually followed by hypothyroidism.
- Radiation-induced painless thyroiditis with hyperthyroxinemia is an uncommon side effect of external beam radiotherapy to the head and neck area. Transient hyperthyroidism is also followed by hypothyroidism.
- Thyroid metastasis occurs in 1.25–24.00% of patients with metastatic carcinoma; however, thyrotoxicosis owing to follicular destruction by metastasis is rare.
- Structural homology in the human chorionic gonadotropin and TSH molecules as well as receptors provides the biochemical basis for the ability of human chorionic gonadotropin to stimulate the TSH receptor. Trophoblastic tumors, hydatidiform moles, and choriocarcinomas secrete human chorionic gonadotropin in large amounts, often causing hyperthyroidism. Hyperthyroidism is likely for human chorionic gonadotropin level >200 IU/mL.

Removal or effective therapy for the underlying tumor is the most effective therapy for clinical syndromes caused by excessive β-HCG production. Hyperthyroidism can be treated short term with thionamide therapy if there is belief that chemotherapy or other strategies to treat the underlying malignancy are likely to be effective. In patients with less responsive tumors, thyroidectomy or radioactive iodine may be required.

Symptoms Thyrotoxicosis is characterized by a hyperadrenergic state. Sinus tachycardia, systolic flow murmur, and water-hammer pulse are common. Atrial dysrhythmias (atrial

fibrillation, atrial flutter, and premature atrial contractions) and congestive heart failure are often observed. Eye signs include exophthalmos, lid lag, and upper lid retraction. Neuropsychiatric symptoms include agitation, anxiety, restlessness, fear, paranoia, and mood swings. Neuromuscular symptoms include fine tremor in the hands and proximal myopathy (common in the elderly). Gastrointestinal symptoms include hyperphagia, diarrhea, nausea, vomiting, and abdominal pain. Skin signs include flushed skin, hair loss, and pretibial myxedema. Apathetic hyperthyroidism is seen in the elderly with prominent features of congestive heart failure, atrial fibrillation, and weight loss.

Diagnosis Thyrotoxicosis is diagnosed by measuring thyroid hormone (thyroxin and triiodothyronine) and TSH levels. Measurement of free thyroid hormones instead of total serum hormone prevents changes introduced by variations in thyroxine-binding globulin. Pituitary and hypothalamic causes of thyrotoxicosis are very rare. Measurements of thyroid-stimulating immunoglobulin and anti-thyroperoxidase antibodies are helpful in evaluating autoimmune etiologies. A radionuclide scan is helpful in distinguishing hyperfunction of the thyroid gland from thyroiditis.

Thyroid storm should be considered in the differential diagnosis of hyperpyrexia in the emergency care setting, particularly in cancer patients with risk factors for Graves disease (e.g., bioimmunotherapy and history of irradiation of the neck or chest area) or tumors that may secrete human chorionic gonadotropin. A scoring system for thyroid storm and a set of diagnostic criteria, including fever, tachycardia, tachyarrhythmias, and mental status changes, have been proposed [67, 68].

Management:

- Treatment of Graves disease includes anti-thyroid medications, radioactive iodine, and surgery.
- Treatment of thyroiditis primarily involves removing the causative factors and controlling the hyperadrenergic symptoms with β-blockers.
- If thyroid storm is highly likely on the basis of clinical criteria, diagnostic studies should be performed, and therapy should be initiated immediately. In addition to support for systemic decompensation and correction of precipitating factors, acute management may involve the following:
  - Propylthiouracil 100–600 mg/day or methimazole 10–60 mg/day.
  - β-blockers, both cardioselective and noncardioselective, are important adjuncts in treating hyperthyroidism. β-blockade provides rapid relief of hyperadrenergic symptoms and signs of thyrotoxicosis. High doses of propranolol (greater than 160 mg/day) can inhibit peripheral conversion of T4 to T3.
  - Saturated solution potassium iodide (3–5 drops) is administered orally every 8 hours to block release of thyroid hormones in patients with thyrotoxicosis. At pharmacologic concentrations (100 times the normal plasma level), iodides decrease thyroid gland activity through the Wolff-Chaikoff effect.
  - The oral contrast agents also are potent inhibitors of T4-to-T3 conversion, making them ideal for treatment of severe or decompensated thyrotoxicosis. They are generally given after starting treatment with thioamide. Although physicians have used IV iodinated radiographic contrast medium to treat a case of thyroid storm, this approach is highly nephrotoxic, and its efficacy has yet to be firmly established.
  - Other treatment options include corticosteroids (e.g., dexamethasone, which inhibits peripheral thyroxine conversion), colestipol, lithium, amiodarone, ipodate, iopanoic acid, and potassium perchlorate.
  - Plasmapheresis and hemoperfusion are effective ways to remove excess thyroid hormone.

Myxedema Coma

The prevalence of hypothyroidism is 2–3% in the general population with a female-to-male ratio of 10:1. Therefore, female cancer patients with preexisting or co-existing hypothyroidism are common. Hypothyroidism may also be a complication of cancer or its treatment.

Causes:

- Total or near-total thyroidectomy may be performed for a variety of oncologic reasons in the management of thyroid cancer, head and neck cancer, or thyroid metastasis. Thyroid replacement is needed in this group of patients.
- Irradiation can cause primary, secondary, or tertiary hypothyroidism.
- Primary hypothyroidism is caused by thyroid cell destruction, inhibition of cell division, vascular damage, and possibly an immune-mediated phenomenon. Factors that increase the risk of developing primary hypothyroidism include a high radiation dose to the vicinity of the thyroid gland, duration since therapy, lack of shielding of the thyroid during therapy, and combined irradiation and surgical treatments [69].
- Hypothyroidism after radiation therapy is related to the radiation dose. The threshold for causing clinical hypothyroidism is about 10 Gy [66, 70].
- Chemotherapy
  - The incidence of primary hypothyroidism is increased in patients treated with multiple combination drug regimens [71, 72], with or without radiation [71].

  - L-Asparaginase, in addition to inhibition of TBG synthesis discussed above, may also inhibit TSH synthesis reversibly and lead to temporary hypothyroidism with decreased free T_4 levels [73].
- Immunotherapy
  - Thyroid dysfunction is a recognized side effect of cytokine treatments. Treatment with interleukin-2 produces thyroid dysfunction in approximately 20–35% of patients [74]. These patients have hypothyroidism, hyperthyroidism, or hyperthyroidism followed by hypothyroidism [75]. Approximately 10% of interferon-treated patients develop primary hypothyroidism [76]. Patients with anti-thyroid antibodies before therapy are at higher risk of cytokine-induced thyroid dysfunction.
  - Immune checkpoint inhibitors induce immune thyroiditis. In the late phase of thyroiditis, long-term or permanent hypothyroidism results.
- Targeted therapy
  - Bexarotene (a retinoid X receptor [RXR]-selective ligand to treat cutaneous T-cell lymphoma) caused secondary hypothyroidism dose-dependently [77]. In addition to suppressing transcription of TSH by an RXR-mediated thyroid hormone-independent mechanism [78], bexarotene also increases clearance of thyroid hormones by a metabolic pathway not involving deiodinase [79].
  - Many TKIs (e.g., pazopanib, nilotinib, axitinib, cabozantinib, sorafenib, dasatinib, sunitinib, and imatinib) may cause primary hypothyroidism. Tyrosine kinase receptors (e.g., VEGFR, EGFR, RET, KIT, MET) and downstream signaling pathways (e.g., BRAF, PI3K, and mTOR pathways), especially RET and BRAF, play important roles in thyroid physiology. Imatinib and sunitinib may have additional mechanisms for inhibition of thyroid function. These inhibitors inhibit different targets with varying potencies/selectivity, and relative contribution of inhibition of specific pathways or specific etiologic mechanisms may vary.
  - Using high-dose (100–1000 mCi) [^{131}I]-metaiodobenzylguanidine to treat unresectable pheochromocytoma may result in primary hypothyroidism.

Symptoms Hypothyroid symptoms are nonspecific and include fatigue, general weakness, cold intolerance, depression, weight gain, joint aches, constipation, dry skin, and menstrual irregularities. Signs of moderate to severe hypothyroidism include hypertension, bradycardia, coarse hair, periorbital edema, carpal tunnel syndrome, and delayed relaxation of the tendon reflexes. Unusual signs of severe hypothyroidism include megacolon, cardiomegaly, and congestive heart failure.

Myxedema coma may occur in patients with hypothyroidism and be life-threatening as the severity of hypothermia, bradycardia, and hypoventilation increases. Pericardial, pleural, and peritoneal effusions are often present. An ileus is present in about two thirds of cases. Central nervous system changes in these patients include seizures, stupor, and coma.

Diagnosis The diagnosis of hypothyroidism is confirmed by thyroid function tests. Myxedema coma is rare since screening for thyroid dysfunction in cancer patients on targeted therapy or immunotherapy is routine. In most cases, TSH and free T4 testing is adequate for initial evaluation. In patients with myxedema coma, serum thyroid hormone levels are usually very low, whereas the TSH level is quite high (except in cases of secondary hypothyroidism).

Anemia, hyponatremia, hypoglycemia, hypothermia, and hypotension can occur. Arterial blood gas measurement usually reveals retention of carbon dioxide and hypoxemia. An EKG often shows sinus bradycardia, various types and degrees of heart block, low voltage, and T-wave flattening.

Management Recognition of hypothyroidism may be difficult in the emergency care setting. Thyroid function test results typically are not available expeditiously. The emergency physician's responsibility is to consider the diagnosis of hypothyroidism, provide acute care, and order the appropriate thyroid function tests to expedite diagnosis. Myxedema coma occurs most often in elderly hypothyroidism patients with a superimposed precipitating event, which must also be treated.

Rapid clinical diagnosis with early therapy may be lifesaving. In critically ill patients, if free thyroxine is very low and myxedema coma is highly suspected, 0.3–0.5 mg of levothyroxine should be given IV once, followed by 0.025–0.100 mg/day. Other supportive measures, such as correction of hypothermia using slow rewarming and ventilatory and circulatory support, are critical.

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Nephrology

30

Amit Lahoti

Case Study

A 70-year-old woman with a history of ovarian cancer s/p debulking surgery was started on chemotherapy with carboplatin and paclitaxel. Bevacizumab was added to the last 6 chemotherapy cycles. The patient developed relative thrombocytopenia with a drop in the platelet count from 276 to 71 K/μL. Nifedipine XL 60 mg PO daily was added to bisoprolol 10 mg PO daily due to worsening blood pressure. The patient was subsequently evaluated in the emergency department due to elevated blood pressure (BP 216/93) and worsening renal function. Serum creatinine increased from a baseline of 1.2–1.9 mg/dL. She was treated with clonidine and hydralazine and admitted to the hospital with a presumptive diagnosis of drug-induced thrombotic microangiopathy due to bevacizumab (anti-VEGF therapy) and further treatment was withheld. However, the serum creatinine continued to increase over the next 5 months to 4.5 mg/dL. A renal biopsy was performed at that time which confirmed acute thrombotic microangiopathy (TMA). Since she had persistent disease despite stopping bevacizumab therapy, she was started on eculizumab, a terminal complement inhibitor. After 6 months of therapy, the serum creatinine stabilized at 2.6 mg/dL. Platelet count recovered to 273 K/μL. She has remained off of eculizumab for over 1 year with no evidence of recurrence of TMA.

Chapter Overview

Renal emergencies are common during the care of patients with cancer and require a multidisciplinary approach between the emergency physician, nephrologist, oncologist, and interventional radiologist. Acute kidney injury (AKI) is a frequent complication of cancer treatment associated with a higher mortality rate and hospital length of stay. General causes of AKI such as acute tubular necrosis and hypovolemia are still common in patients with cancer. However, there are other etiologies of AKI that are more specific to cancer, such as AKI in the setting of multiple myeloma, stem cell transplant, tumor lysis syndrome, targeted therapy, and immunotherapy. Patients with cancer may also present with severe electrolyte derangements requiring immediate treatment by the emergency physician.

Introduction

The kidneys are important in regulating electrolyte and acid-base levels, eliminating waste products and fluid, and producing enzymes and hormones. Compared to other organs, the kidneys receive the highest amount of blood supply from the heart on a per-gram basis. Therefore, the kidneys are vulnerable to AKI from toxins, drugs, or metabolites circulating in the bloodstream. Advances in conventional chemotherapy, targeted therapy, and immunotherapy have improved the overall survival of patients with cancer. However, many of these therapies entail a higher risk of AKI. Prevention is essential since there is no effective therapy available for AKI. This chapter emphasizes some of the more common renal problems that emergency physicians encounter during cancer treatment.

Acute Kidney Injury in Cancer Patients

The incidence of AKI in the setting of cancer varies with the underlying population, tumor type, and treatment. A 7-year study in Denmark examining the incidence of AKI among 37,267 patients with cancer reported a rate of 17.5% within 1 year of cancer diagnosis [1]. Long-term dialysis was required in 5.1% of patients developing AKI. However, other studies involving higher risk, critically ill patients report the

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need for dialysis in up to 60% of patients with AKI. Patients with renal cell carcinoma, hepatocellular carcinoma, multiple myeloma, lymphoma, and leukemia were at highest risk of AKI. A Canadian study between 2007 and 2014 found the overall cumulative incidence of AKI among 163,071 patients undergoing cancer treatment to be 9.3% [2]. Patients with myeloma, bladder cancer, and leukemia were at highest risk. The annual incidence of AKI also increased from 18 to 52 per 1000 person-years during that time period. Development of AKI correlates with increased hospital length of stay, health-care costs, and mortality rates [3]. AKI increases the toxic effects of chemotherapy, excludes patients from clinical trials, and limits further cancer treatment. The causes of AKI are generally classified into three main categories: renal hypoperfusion, intrinsic renal disease, and postrenal obstruction (Table 30.1).

Varying definitions of AKI have been historically used in patient care and clinical research. In 2004, a standard classification termed the Risk, Injury, Failure, Loss, End-Stage (RIFLE) criteria was proposed based on relative rise in serum creatinine (SCr) or progressive oliguria [4]. A 50% rise in SCr from baseline defined the earliest stage of AKI. The criteria were recently modified by the Kidney Disease Improving Global Outcomes (KDIGO) AKI Workgroup to include even smaller increases in SCr (>= 0.3 mg/dL) as well as a time constraint for the rise in creatinine elevation (Table 30.2). While decreased urine output is also part of the definition, it is often cumbersome to measure and not used as routinely. The KDIGO criteria for AKI are now universally accepted both in clinical practice and research. AKI as defined by RIFLE or KDIGO has been validated as a negative prognostic marker [5, 6]. In a study of patients with newly diagnosed AML undergoing induction chemotherapy, there was a stepwise increase in mortality associated with the no-AKI, Risk, Injury, and Failure categories (3.8%, 13.6%, 19.6%, and 61.7%, respectively) [7]. Another study of critically ill patients with cancer found a 1.3-, 3.0-, and 14-fold increase in 60-day mortality for the Risk, Injury, and Failure categories, respectively [3]. More recent studies using the KDIGO definition have found a similar stepwise increase in mortality with progressive AKI [8].

A brief clinical exam, routine labs, and optimization of hemodynamics are necessary for patients presenting with AKI upon arrival to the emergency department (ED). Volume depletion can manifest by orthostatic hypotension, tachycardia, poor skin turgor, dry mucous membranes, and low central venous pressure. Intravenous (IV) hydration, preferably with crystalloid solutions, should be given to target a mean arterial pressure greater than 65 mmHg. Patients with prerenal azotemia may have a blood urea nitrogen-SCr ratio greater than 20, a fractional excretion of sodium less than 1%, a urine sodium level less than 20 mEq/L, and the presence of hyaline casts. A fractional excretion of sodium greater than 2%, a urine sodium level greater than 40 mEq/L, and the presence of coarse granular casts are suggestive of acute tubular necrosis. Acute interstitial nephritis is a common cause of AKI in patients with cancer given the high

Table 30.1 Common causes of acute kidney injury in patients with cancer

Renal hypoperfusion
Volume depletion
Nausea, vomiting, diarrhea
Decreased oral intake due to mucositis (5-fluorouracil, methotrexate, taxanes)
Polyuria caused by hyperglycemia (steroids) or diabetes insipidus (pituitary tumor)
"Third spacing" (hypoalbuminemia, liver or peritoneal metastases, interleukin 2)
Insensible loss of fluid from skin lesions (mycosis fungoides)
Hemodynamic mediated
Sepsis
Renal arteriolar vasoconstriction (NSAIDs, calcineurin inhibitors, hypercalcemia)
Congestive heart failure
Hepatorenal syndrome/hepatic sinusoidal obstruction syndrome
Budd-Chiari syndrome
Intrahepatic inferior vena cava compression or thrombosis caused by hepatomegaly or a tumor
IV iodinated contrast agent
Abdominal compartment syndrome
Intrinsic renal disease
Acute tubular necrosis
Chemotherapy (cisplatin, ifosfamide)
Anti-infectives (amphotericin B, foscarnet, cidofovir, aminoglycosides, vancomycin)
Bisphosphonates
Sepsis
Prolonged prerenal azotemia
Acute interstitial nephritis (penicillins, cephalosporins, fluoroquinolones, NSAIDs, checkpoint inhibitors)
Crystal nephropathy (methotrexate, acyclovir, ciprofloxacin, sulfonamides, rifampin)
Osmotic nephrosis (IV immunoglobulin, mannitol, starch)
Thrombotic microangiopathy (post-HSCT, gemcitabine, anti-VEGF therapy, prior radiation therapy)
Myeloma-related kidney disease
Tumor lysis syndrome
Tumor infiltration of the kidney
Glomerulonephritis
Lysozymuria (CMML or AML) with direct tubular injury
Cytokine release syndrome (engraftment syndrome, CAR T-cell therapy)
Postrenal obstruction
Bladder outlet obstruction (malignancy of the cervix, prostate, bladder, or uterus)
Retroperitoneal disease (metastasis, lymphadenopathy, fibrosis)
Hemorrhagic cystitis (cyclophosphamide, BK* virus, adenovirus)
Ureteral strictures (prior radiation therapy, BK virus)

HSCT hematopoietic stem cell transplantation, *VEGF* vascular endothelial growth factor, *CMML* chronic myelomonocytic leukemia, *AML* acute myeloid leukemia, *CAR* chimeric antigen receptor
[a]Initials of the patient in whom it was first detected in 1971

Table 30.2 Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI (https://kdigo.org/guidelines/acute-kidney-injury/)

KDIGO stage (corresponding RIFLE stage)	Increase in creatinine level	Decrease in urine output
1 (Risk)	≥50% from baseline within 7 days or ≥0.3 mg/dL within 48 h	<0.5 mL/kg/h × 6 h
2 (Injury)	≥100% from baseline	<0.5 mL/kg/h × 12 h
3 (Failure)	≥200% from baseline, absolute SCr level ≥4 mg/dL with acute rise ≥0.5 mg/dL, or need for dialysis	<0.3 mL/kg/h × 24 h or anuria × 12 h

usage of antibiotics, NSAIDs, proton pump inhibitors, and immune checkpoint inhibitors. Acute interstitial nephritis is likely under-diagnosed, as patients may not present with classic hypersensitivity reactions such as fever, rash, or eosinophilia. Patients with severe bladder outlet obstruction can present with suprapubic pain and a palpable bladder. The use of a portable bladder scanner quickly confirms obstruction by measuring a post-void residual urine volume greater than 100 mL. Renal ultrasonography is sensitive in detecting hydronephrosis, although this characteristic finding of urinary tract obstruction may not be apparent in patients with significant retroperitoneal disease or in the setting of early obstruction.

There has been much controversy as to the optimal solution for fluid resuscitation of the patient with AKI, especially in the setting of sepsis. Mechanisms to maintain renal blood flow through autoregulation are impaired in the setting of AKI. While initial use of fluids to optimize cardiac output is beneficial, prolonged use can lead to harm from fluid overload. A fine balance is often necessary between fluids and vasopressors, as several retrospective studies associate fluid overload with increased mortality [9]. Colloid solutions such as IV albumin and starch have not proven to be more effective than crystalloid solutions and are considerably more expensive [10]. Intravenous starch may cause AKI by inducing osmotic nephrosis of the renal tubules; thus, in general, its use should be avoided in patients with AKI. Albumin and starch leak out of the intravascular compartment within hours after administration, thereby potentially worsening peripheral edema. However, patients with cirrhosis can benefit from IV albumin in the setting of sepsis or large volume paracentesis. We generally prefer using crystalloid solutions such as isotonic saline (0.9% saline) for volume resuscitation. Interestingly, animal studies have demonstrated vasoconstriction of the renal arteries from chloride-containing solutions, which could theoretically worsen renal function. However, balanced (low-chloride) crystalloid fluids such as Plasma-Lyte or lactated Ringer's solution have not consistently demonstrated better outcomes when compared to normal saline [11–13]. Early goal-directed therapy (EGDT) for sepsis (protocol-driven fluid resuscitation, transfusions, inotropes, and vasopressor support) showed promise in a single-center RCT [14], but did not decrease mortality or need for renal replacement therapy (RRT) in three subsequent larger RCTs [15–17]. Furthermore, a meta-analysis of individual patient data demonstrated that EGDT had equivalent outcomes but higher hospitalization costs when compared to standard of care [18]. Continuous infusion of norepinephrine (2–12 μg/min) or vasopressin (0.01–0.04 U/min) is generally used if fluid resuscitation alone is unable to maintain a target mean arterial pressure of 65 mmHg. Placement of a Foley catheter should be considered if the patient has signs of bladder outlet obstruction or urinary retention. Emergent placement of a percutaneous nephrostomy (PCN) tube may be necessary if the site of obstruction is above the level of the bladder outlet. The use of nephrotoxic medications and iodinated contrast agents should be avoided, if possible.

RRT is indicated in patients who present with persistent hyperkalemia, fluid overload refractory to diuretics, severe metabolic acidosis, uremia, or marked tumor lysis syndrome (TLS). Early nephrology consultation from the ED expedites dialysis in these patients. Intermittent hemodialysis (IHD) is generally sufficient for volume and metabolic clearance in patients who are hemodynamically stable; however, patients with septic shock or hemodynamic instability may require continuous renal replacement therapy (CRRT) in the intensive care unit. In patients with sepsis and AKI, the use of CRRT has not demonstrated a survival advantage over IHD but can be more effective in minimizing fluid overload [19, 20].

AKI and Conventional Chemotherapy

The most common cause of AKI due to conventional chemotherapy is acute tubular necrosis (ATN). Offending drugs include platinum agents (cisplatin and carboplatin), ifosfamide, and pemetrexed. Cisplatin can cause ATN, thrombotic microangiopathy, and hypomagnesemia. Carboplatin is much less injurious to the kidneys but may still cause ATN and hypomagnesemia. Injury from platinum drugs is generally dose dependent and can lead to chronic kidney disease despite drug discontinuation. ATN from ifosfamide can lead to progressive decline in renal function over several years. Severe injury from ifosfamide manifests as Fanconi's syndrome (hypokalemia, hypophosphatemia, acidosis, and glucosuria), which may persist long after discontinuation of therapy. Pemetrexed, a derivative of methotrexate, can be associated with ATN and diabetes insipidus. Hydration with isotonic fluid is the mainstay to prevent ATN.

High-dose methotrexate (MTX) ranging from 1 to 15 g/m^2 can precipitate in the renal tubules leading to obstruction,

inflammation, and AKI. Bicarbonate-based intravenous fluids help to clear MTX crystals in the urine by increasing its solubility. Although dialysis lowers serum MTX levels, the effect is temporary due to the high level of protein binding and rebound of serum levels. In patients with impaired renal function, glucarpidase can be administered to metabolize MTX into two inactive compounds that are subsequently cleared by the liver.

Endothelial injury due to gemcitabine, mitomycin C, and cisplatin leads to activation of complement and generation of thrombi within the renal microvasculature leading to thrombotic microangiopathy (TMA). This diagnosis should be suspected in patients with Coombs (−) hemolytic anemia, thrombocytopenia, and AKI. Treatment includes holding the offending drug and possibly the use of complement inhibitors.

AKI and Immunotherapy

Immunotherapy, which is based on regulating the immune system to recognize and eradicate tumor cells, is currently used in the treatment of malignant melanoma, Hodgkin's lymphoma, renal cell and urothelial carcinoma, non-small cell lung cancer, and head/neck cancer. Immune checkpoint inhibitors (ICIs) release inhibition of T-lymphocytes to generate a long-lasting anti-tumor response. Current ICIs target cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1(PD-L1). Renal toxicity occurs in approximately 2% of patients and increases to 5% for patients on dual therapy [21]. This renal injury is usually granulomatous interstitial nephritis, but less commonly presents as lupus-like nephritis, pauci-immune glomerulonephritis, IgA nephropathy, and focal segmental glomerulosclerosis. Onset of kidney disease varies anywhere from 1 to 8 months after initiation of therapy and up to 2 months after the last dose. Nephritis should be considered in any patient treated with ICIs and presenting with AKI, proteinuria, or hematuria. Early administration of steroids should be considered.

AKI and Anti-VEGF Therapy

Angiogenesis inhibition by blocking vascular endothelial growth factor (VEGF) or its receptor inhibits endothelial cell proliferation and vessel formation. Side effects include proteinuria, hypertension, and renal-limited thrombotic microangiopathy in severe cases. Proteinuria due to compromise of the filtration barrier of the nephron ranges from mild to fulminant nephrotic syndrome. Hypertension is mediated by decreased nitrous oxide levels leading to endothelial dysfunction. First-line agents for treatment of hypertension include angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), while calcium channel blockers are suitable alternatives. Centrally acting drugs or diuretics may be added for a goal blood pressure less than 140/90 mm Hg. Patients who develop hypertensive crisis or encephalopathy should discontinue anti-VEGF therapy immediately and admitted to the ICU. Patients who develop TMA in the setting of anti-VEGF therapy will present with de novo hypertension and unexplained renal failure. TMA can resolve with time after withholding further therapy, although some patients will benefit from anti-complement therapy such as eculizumab.

Chronic Kidney Disease in Cancer Patients

The prevalence of CKD ranges from 12% to 53% at the time of cancer diagnosis [22, 23]. Older patients with cancer have a relatively higher incidence of hypertension and diabetes, which are the two most common risk factors for CKD. Cancer therapy is also associated with progressive CKD. A retrospective study of patients with solid tumors demonstrated a reduction in eGFR of 13 mL/min/1.73 m^2 after 2 years, and 17.7% of patients with CKD stage II advanced to stage III or IV [23]. The incidence of CKD is even higher in patients with kidney cancer and bladder cancer (28.7% and 46%, respectively) [24, 25].

Glomerular filtration rate (GFR) as measured by inulin or iohexol clearance is the gold standard for measurement of kidney function but is difficult to perform in the clinical setting. Therefore, the estimated GFR (eGFR) as calculated by formulas using SCr, age, gender, and race is commonly reported by most hospital laboratories. Estimates of GFR as measured by the Modification of Diet in Renal Disease (MDRD) [26] and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [27] equations are felt to be most accurate, and have largely supplanted the older Cockcroft Gault (CG) equation [28]. However, most pharmacokinetic studies of drugs were based on the CG equation. It is important to remember several caveats concerning estimating equations for GFR. Ninety percent of patients will have a true GFR within 30% of their eGFR. The equations are less valid in patients with extremes in body mass. Additionally, they tend to underestimate GFR in patients with normal or near-normal SCr levels. Most importantly, these equations are not reliable estimates when the SCr is not in steady state as seen in AKI. It should be assumed that any patient that has oliguric AKI unresponsive to hydration has a GFR <10 ml/min *regardless* of the SCr level.

Most estimates of glomerular filtration rate (eGFR) are based on SCr levels that are affected by many different factors. Elevation in SCr is a relatively late marker of CKD, and only manifests after a 50% decline in glomerular filtration

rate. Reduced creatinine production due to acute illness and sarcopenia, as well as creatinine dilution during volume overload, can further complicate the estimation of renal function in patients with cancer.

Multiple Myeloma and AKI

Multiple myeloma is a clonal malignancy of plasma cells that results in the overproduction of immunoglobulins, their fragments, or free light chains that circulate in the blood (paraproteins). These paraproteins cause injury by depositing in peripheral organs such as the heart, kidney, and liver. AKI from paraprotein deposition in the kidneys is often the initial presentation of patients with multiple myeloma. Cast formation in the distal tubule occurs when paraproteins filter through the glomeruli and bind to Tamm-Horsfall mucoprotein causing obstruction, tubular injury, and inflammation. Amyloid light chain amyloidosis (AL amyloidosis) develops when paraproteins undergo conformational changes and deposit as microscopic fibrils in the glomeruli and vessels. Light chains or heavy chains are deposited within the glomerular and tubular basement membranes, leading to monoclonal immunoglobulin deposition disease (MIDD).

The clinical presentation of AKI in patients with multiple myeloma varies from asymptomatic proteinuria to nephrotic syndrome and rapidly progressive renal failure. AKI is diagnosed in more than half of all patients with multiple myeloma at initial presentation, of which 10% require dialysis. Multiple myeloma should always be part of the differential diagnosis in elderly patients with unexplained acute or chronic kidney disease. Initial workup for multiple myeloma consists of serum and urine protein electrophoresis, immunofixation electrophoresis, and serum-free light chain assays to detect a monoclonal protein. Monoclonal proteins in the urine (Bence-Jones proteins) are not detected by routine qualitative dipstick urinalysis, which detects mainly albuminuria. However, paraprotein deposits from MIDD and AL amyloidosis can damage the filtration barrier of the glomerulus, leading to significant albuminuria detectable on dipstick urinalysis. In contrast, myeloma cast nephropathy has minimal glomerular involvement and typically presents with only mild albuminuria. Other clinical manifestations from light chain amyloid deposits include restrictive cardiomyopathy, hepatomegaly, carpal tunnel syndrome, and orthostatic hypotension. Definitive diagnosis is confirmed by a renal biopsy revealing characteristic casts, light chains, or amyloid deposits.

Early aggressive treatment of patients presenting with multiple myeloma and renal disease helps stabilize or improve kidney function. Initial hydration consists of normal saline infusion, with a urine output goal of 2.5–3.0 L a day, which helps prevent precipitation of casts within the distal tubule. Steroids are often used initially to decrease the production of paraproteins and alleviate end-organ damage. Aminoglycosides, IV contrast agents, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) exacerbate renal injury and should be avoided. Hypercalcemia commonly occurs in patients with multiple myeloma and aggravates acute kidney injury. If hypercalcemia does not resolve with the use of hydration and calcitonin, therapy with a bisphosphonate should be considered (e.g., 3–4 mg of zoledronic acid diluted in 100 mL of normal saline administered in an IV infusion for at least 15 min). Plasmapheresis to remove circulating paraproteins has not been shown to improve clinical outcomes. Similarly, the use of high-cutoff filters in hemodialysis, which is much more effective in removing paraproteins than plasmapheresis, does not definitely improve outcomes when used concurrently with effective chemotherapy [29, 30].

Hematopoietic Stem Cell Transplantation (HSCT) and AKI

AKI is a frequent complication of HSCT and has an incidence between 10% and 73% depending on the type of transplant and conditioning regimen [31]. Risk factors include older age, female gender, allogeneic transplant, myeloablative regimen, graft versus host disease (GVHD), hypertension, diabetes, and preexisting CKD. Common causes of AKI include nephrotoxic drugs (e.g., calcineurin inhibitors, foscarnet, amphotericin), sepsis, volume depletion, hepatic sinusoidal obstruction syndrome (HSOS), thrombotic microangiopathy (TMA), and viral nephritis (e.g., BK virus, adenovirus).

Workup in the ED should include a thorough search for nephrotoxic medications and assessment of volume status. A urinalysis, urine protein/creatinine (UPC) ratio, urine sodium, and urine creatinine help determine the etiology of AKI. A low urine sodium level <20 meq/L or fractional excretion of sodium (FENa) <1% suggests volume depletion. Patients with GVHD of the GI tract can present with prerenal azotemia due to vomiting and diarrhea.

HSOS occurs due to endothelial damage of the liver sinusoids from the conditioning regimen given prior to transplant. Patients with HSOS generally present early after HSCT with jaundice, right upper quadrant pain, ascites, edema, and hepatorenal syndrome. Other causes of cholestasis such as GVHD, sepsis, fungal infection, and TPN should be excluded. Doppler imaging of the portal vein in the setting of HSOS reveals reversal of flow. Initial management includes sodium restriction and diuretics, while RRT will be necessary for severe cases.

Viral infections of the genitourinary tract (e.g., adenovirus, BK virus) cause gross hematuria and bladder outlet

obstruction from clots. A three-way urethral catheter should be inserted for continuous bladder irrigation, and urologic consultation should be obtained. Measurement of serum and urine BK and adenovirus levels by PCR should be sent.

Paraneoplastic glomerular disease such as membranous nephropathy or minimal change disease can occur months to years after HSCT while tapering immunosuppression. This diagnosis should be suspected in patients with a history of HSCT that present to the hospital with de novo nephrotic range proteinuria and edema. Symptoms are initially managed with diuretics, but renal biopsy is required for definitive diagnosis.

Electrolyte Abnormalities

Tumor Lysis Syndrome (TLS)

TLS is a common life-threatening emergency in patients with cancer presenting to the ED. Tumor cells rapidly release potassium, phosphorus, and uric acid into the extracellular space and overwhelm the excretory capacity of the kidneys. Hyperkalemia predisposes patients to cardiac dysrhythmias and sudden death. Hyperphosphatemia and secondary hypocalcemia may lead to AKI, muscular irritability, cardiac dysrhythmias, and metastatic calcification. Uric acid precipitating as crystals in the renal tubules causes obstruction, vasoconstriction, and inflammation. Patients with rapidly proliferating chemosensitive hematologic malignancies are at the greatest risk for TLS. Risk factors for TLS include a white blood cell count greater than 50,000/μL, elevated lactate dehydrogenase level, bulky disease, marrow or organ infiltration, advanced age, and chronic kidney disease. Cases of TLS in patients with a solid tumor undergoing chemotherapy and/or radiation therapy have been reported; however, patients with non-Hodgkin's lymphoma or acute leukemia are at greatest risk.

The identification of TLS is generally straightforward in patients who present with marked derangements in electrolyte levels. However, patients with impaired renal function secondary to an effective prerenal state, such as volume depletion or hypotension, can also develop hyperkalemia, hyperphosphatemia, and hyperuricemia. Unlike patients with TLS, patients with prerenal azotemia will rapid normalize electrolyte levels and renal function with hydration and optimization of blood pressure.

Intravenous hydration to maintain adequate urine output and xanthine oxide inhibitors (allopurinol or febuxostat) to prevent the formation of uric acid are the mainstays of preventing TLS. Infusion of isotonic saline should be instituted 24 h prior to chemotherapy at 100 mL/m^2/h and titrated accordingly to maintain a urine output of at least 2.5 L a day. Conservative fluid management strategies are necessary in patients with underlying congestive heart failure. High-risk patients or those who have elevated uric acid levels prior to chemotherapy should receive rasburicase (0.2 mg/kg [IV] daily for up to 5 days). Rasburicase converts uric acid to allantoin, which is 5–10 times more soluble in the urine. Fixed dosing of rasburicase (3 or 6 mg) up to 2 doses has been shown to be just as effective as weight-based dosing and leads to significant cost savings [32]. Rasburicase causes production of hydrogen peroxide that can cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Patients at risk should have G6PD levels checked prior to receiving rasburicase.

Management of established TLS also consists of judicious hydration as well as rasburicase for hyperuricemia. Alkalization of the urine retards the formation of uric acid crystals but increases the risk of calcium phosphate crystal deposition. Therefore, routine urine alkalization in patients with TLS is no longer recommended. Nephrology consultation should be sought for patients presenting to the EC with TLS who have peaked T waves on electrocardiogram (EKG), dysrhythmias, or oliguria. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and NSAIDs should be avoided in patients with TLS because they worsen hyperkalemia and AKI. Although some patients deemed high risk of developing severe TLS have been preemptively started on CRRT prior to chemotherapy, this is not standard practice. Pseudohyperkalemia occurs in the setting of extreme leukocytosis, due to spurious elevations in serum potassium levels resulting from ex vivo lysis of white blood cells. The diagnosis should be considered in patients without other signs of TLS and the absence of EKG changes suggestive of hyperkalemia. If a patient is suspected of having pseudohyperkalemia, potassium level should be measured on a heparinized plasma sample placed on ice or on the whole blood by a point-of-care analyzer.

Hyponatremia

Hyponatremia (serum sodium levels less than 135 mEq/L) has been reported in 14–23% of patients with cancer on admission to the hospital. Increased hyponatremia severity is a negative prognostic factor for survival in patients with non-small cell lung cancer, renal cell carcinoma, gastric cancer, and non-Hodgkin's lymphoma. The two most frequent causes of hyponatremia in patients with cancer are hypovolemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH). Common etiologies of SIADH include malignancy (e.g., the lung, gastrointestinal, central nervous system), pneumonia, drugs (e.g., antidepressants, haloperidol, carbamazepine, cyclophosphamide, platinum compounds, vinca alkaloids), nausea, and pain. Other considerations when assessing patients with hyponatremia in

the setting of cancer include renal salt wasting secondary to chemotherapy, "tea and toast syndrome" resulting from malnutrition, water intoxication, and adrenal insufficiency secondary to adrenal metastases or steroid withdrawal.

Symptoms in patients with hyponatremia may be absent, mild (confusion, dizziness, nausea, and lethargy), or severe (seizures, coma, and death). The occurrence of symptoms depends primarily on the rate of decline in the serum sodium level as opposed to the absolute level. Adaptation of the brain to hyponatremia occurs gradually by the excretion of osmolytes from cells to prevent cerebral edema. Cerebral edema with eventual brain stem herniation is a risk if the rate of decline in serum sodium level outpaces the excretion of osmolytes. Immediate treatment is required to raise the serum sodium level until the patient is asymptomatic. If the decline in serum sodium level is more gradual, the patient may be asymptomatic or have only mild symptoms. Rapid correction of hyponatremia is not indicated in this situation.

Initial workup for hyponatremia should include a physical examination to assess the patient's volume status, chemistry profile, plasma osmolality, urine electrolyte levels, and urine osmolality. Patients with volume depletion generally have urine sodium levels less than 20 mEq/L and concentrated urine (urine osmolality greater than plasma osmolality). Patients with hypervolemia (those with heart failure, cirrhosis, third spacing caused by peritoneal or liver metastases, hypoalbuminemia, or inferior vena cava compression or obstruction) have signs of fluid overload upon physical examination (e.g., edema, ascites, effusions) but are in an effectively prerenal state. Therefore, they also will have urine sodium levels less than 20 mEq/L and concentrated urine. Patients with SIADH have urine sodium levels greater than 40 mEq/L and inappropriately dilute urine (urine osmolality less than plasma osmolality). Patients with "tea and toast syndrome" have serum sodium levels less than 20 mEq/L and appropriately dilute urine (urine osmolality less than plasma osmolality). Urine sodium levels are variable in patients with water intoxication, but urine osmolality is appropriately dilute, typically less than 150 mOsm/kg.

Urgent treatment is not indicated for hyponatremic patients who are asymptomatic or have only mild symptoms. Rapid correction of hyponatremia in these patients will increase the risk of osmotic demyelination syndrome. Patients with volume depletion should receive isotonic fluids such as normal saline. Otherwise, total fluid intake should be restricted to less than 1 L daily. Loop diuretics should be considered in patients with hypervolemia. The treatment of patients with SIADH consists of fluid restriction, salt tablets (initially, 1 g three times daily) and possibly, loop diuretics. The introduction of vasopressin receptor antagonists has revolutionized treatment of hyponatremia in patients with hypervolemia or SIADH. These drugs block the effect of antidiuretic hormone on the collecting ducts of the kidney, thereby preventing water reabsorption and stimulating water diuresis. Currently, two drugs within this class are available, oral tolvaptan (initially 7.5–15.0 mg daily) and IV conivaptan (20-mg loading dose with 20 mg administered over the ensuing 24 h). Serial sodium levels should be monitored every 4–6 h with a goal correction rate of less than 8 mEq/L in 24 h.

Patients with severe symptoms require more urgent intervention with hypertonic saline and close neurologic monitoring. Treatment consists of infusion of 3% saline at a rate of 0.8 mL/kg/h and initial monitoring of serum sodium levels at least every 2–4 h. Alternatively, 3% saline can be administered as 100 ml bolus over 10 min with repeat dosing as needed. The infusion is continued until the sodium level is greater than 120 mEq/L, symptoms have resolved, or the rate of sodium level correction has exceeded 8 mEq within 24 h. Rates of correction in excess of 10–12 mEq per 24 h causes osmotic demyelination syndrome, which results in altered mental status, quadriparesis, quadriplegia, pseudobulbar palsy, coma, or death. Therefore, frequent neurologic assessments and titration of the 3% saline infusion to prevent overcorrection of hyponatremia are necessary.

Hyperkalemia

Hyperkalemia is a particular concern in patients presenting to the ED, as it can be life threatening. Common causes of hyperkalemia in patients with cancer include AKI, TLS, the use of certain drugs (e.g., calcineurin inhibitors, NSAIDs, angiotensin-converting enzyme inhibitors, trimethoprim-sulfamethoxazole, potassium-sparing diuretics) and metabolic acidosis. In most patients, the etiology is multifactorial.

Most patients with hyperkalemia are clinically asymptomatic unless their potassium levels are very high. Cardiac dysrhythmia is the most concerning manifestation. Electrocardiographic changes progress from peaked T waves, flattened P waves, and widened QRS complexes to eventual sine waves. It should be noted that up to 50% of patients with significant hyperkalemia may not manifest EKG abnormalities. Skeletal muscle weakness should also be present in the setting of severe hyperkalemia. Stabilization of the myocardial membrane with IV administration of calcium gluconate (10 mL of 10% IV) or calcium chloride (2 g over 5 min) to counter the effects of hyperkalemia is imperative. A repeat infusion of calcium may be necessary if EKG changes persist. Temporizing measures that shift potassium to the intracellular space involve administration of regular insulin (10 U intravenous), glucose (50 mL of 50% dextrose intravenous), and nebulized albuterol (20 mg in 4 mL). Sodium bicarbonate administration is helpful in patients with concurrent metabolic acidosis by shifting potassium to

the intracellular space as the acidosis is corrected. If severe hyperkalemia persists despite correction of its underlying cause, an urgent nephrology consultation should be sought as dialysis might be necessary. For patients with milder hyperkalemia, monitoring serial potassium levels after discontinuation of the causative drug is sufficient. Loop diuretics can be administered to patients with adequate renal function to enhance potassium excretion in the urine. Sodium polystyrene sulfonate (15–30 g oral) is commonly given to facilitate potassium elimination from the gut; however, its clinical effectiveness is unproven in clinical studies, and its use is rarely associated with intestinal necrosis [33]. Newer potassium-binding agents, patiromer (K^+/Ca^{2+} exchange) and sodium zirconium cyclosilicate (K^+/Na^+ and H^+ exchange), are now clinically available. These newer agents have a more predictable onset of action with less incidence of diarrhea.

Hypercalcemia

Hypercalcemia occurs in 20–30% of all malignancies and is the most common paraneoplastic syndrome. The majority (~80%) of cases are mediated by production of parathyroid hormone-related peptide (PTHr-P) as seen in squamous cell carcinoma, breast cancer, kidney cancer, prostate cancer, and bladder cancer. Local osteolysis due to cytokine release comprises the remaining cases. Lymphoma may cause upregulation of 1,25-hydroxy vitamin D causing hypercalcemia. Rarely, ectopic PTH production occurs in certain tumors. Hypercalcemia causes AKI by vasoconstriction of the afferent arteriole and hypovolemia from polyuria. Intravenous saline should be started to maintain urine output greater than 100 mL/h. Calcitonin begins to decrease serum calcium levels within 15 min of IM or SC administration and has a peak effect within 4 h. Many patients will require a more durable response with osteoclast inhibitors such as pamidronate or zoledronic acid. Denosumab, an inhibitor of receptor activator of nuclear factor-kappaB (RANK) ligand, also provides a long-lasting response to normalize calcium levels. However, patients can develop profound hypocalcemia several weeks later if they have concurrent vitamin D deficiency.

Key Practice Points

- Patients with renal cell carcinoma, multiple myeloma, leukemia, and lymphoma are at highest risk of developing AKI.
- The KDIGO criteria provide a standardized definition of AKI based on increases in serum creatinine level relative to baseline and have prognostic value in the care of patients with cancer.
- Immune checkpoint inhibitors cause AKI by interstitial nephritis, glomerulonephritis, or vasculitis.
- Renal toxicity from anti-VEGF therapy presents with a spectrum of disease from mild proteinuria to malignant hypertension.
- More than half of all patients with multiple myeloma will initially present with some degree of renal injury, and AKI improves with immediate treatment of the underlying myeloma.
- Treatment of TLS includes aggressive IV hydration, rasburicase for hyperuricemia, and, possibly, dialysis for AKI.
- Vasopressin receptor antagonist drugs have revolutionized the treatment of hyponatremia associated with hypervolemia or SIADH, but administration of 3% saline is still required for patients with hyponatremia and severe symptoms (seizures or coma).
- Hyperkalemia may not manifest clinically until potassium levels are severely elevated, and emergent treatment of it includes IV calcium to stabilize the myocardial membrane, IV insulin with glucose, inhaled beta-agonists, and dialysis in refractory cases.

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Urology

31

Shawn Dason, Cheryl T. Lee, and Ahmad Shabsigh

Case Study

A 72-year-old male smoker presented with lower abdominal pain and an inability to urinate. He endorsed several months of gross hematuria, fatigue, and worsening urinary symptoms. On presentation, he was tachycardic, hypertensive, and had acute renal insufficiency with a creatinine of 4 mg/dL. There were no indications for dialysis. The on-call urologist was contacted early (Fig. 31.1) *and recommended catheterization with a 24-Fr 3-way Foley catheter as they made their way to assess the patient. Catheterization and manual irrigation resulted in evacuation of a significant amount of blood clot along with resolution of pain, tachycardia, and hypertension. Despite 45 min of manual irrigation, significant hematuria and clot continued. A noncontrast CT scan revealed bilateral hydroureteronephrosis with a transition point at the level of the bladder. The bladder was distended with hyperdense material concerning for a large bladder mass or blood clot. The patient was admitted by the urology service for continuous bladder irrigation. The next morning, the patient's hematuria continued and creatinine remained elevated. He was taken to the operating room for an endoscopic assessment and ureteral stent placement. Cystoscopy revealed a large hemorrhagic bladder mass that was completely resected for diagnosis and management of the bleeding. The ureteral orifices were not found and ureteral stents could not be placed. The patient was taken to the interventional radiology suite for bilateral nephrostomy tube placement. Creatinine subsequently normalized although there was a period of post-obstructive diuresis. Pathology from the transurethral resection of his bladder tumor revealed urothelial carcinoma with involvement of the muscularis propria. After his hematuria, elevated creatinine and diuresis normalized, the patient was discharged. He had multidisciplinary consultation for his bladder cancer as an outpatient. Following negative staging scans, he received neoadjuvant chemotherapy with four cycles of gemcitabine and cisplatin with his nephrostomy tubes* in situ. *He then had a radical cystectomy and ileal conduit.*

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Hematuria

Hematuria is a common urologic issue assessed in the emergency department (ED). Hematuria can be divided into gross (or visible) hematuria and microhematuria. While the rate of a cancer diagnosis is 1–3% with microhematuria [1, 2], this rises to 25% with gross hematuria [3]. Discolored urine [4], vaginal bleeding, or rectal bleeding may sometimes mimic hematuria and should be considered. True hematuria can usually be determined by history or examination of the urine. If the diagnosis of hematuria is in question, microscopy can be performed to confirm the presence of visualized red blood cells in the urine.

Microhematuria

Microhematuria refers to red blood cells in the urine visualized on microscopy but not with the naked eye. A threshold of three or more red blood cells per high-powered field is traditionally used to define microhematuria [1]. Although some definitions accept chemical urinalysis (dipstick) findings of blood as being consistent with microhematuria, it is generally thought that microscopy is required due to the potential for dipstick false positives (e.g., myoglobinuria) [5]. Microhematuria in the ED setting can often be an incidental finding as it is present in 6.5% of the general population [1]. Numerous nonpathologic causes exist for microhematuria including instrumentation, dehydration, exercise, menses, and other intraabdominal pathology. Nonetheless, the differential diagnosis for microhematuria includes numerous pathologies and its presence should warrant consideration of a urologic etiology to the presenting

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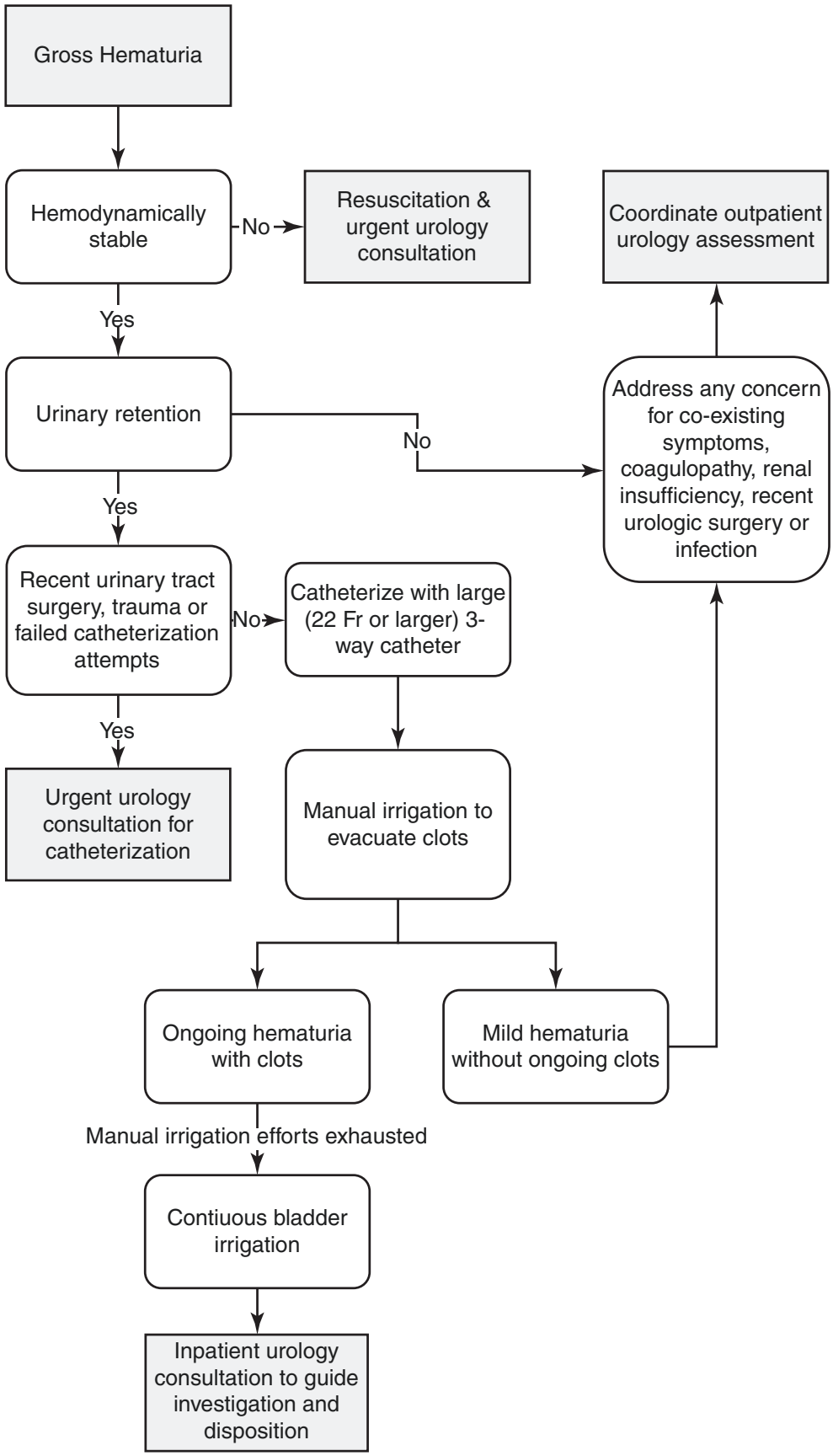

Fig. 31.1 A management algorithm for gross hematuria presenting to the ED. Please refer to the text for additional details

complaint. Microhematuria associated with proteinuria, casts, hypertension, or renal dysfunction should also prompt a nephrologic workup [1]. While microhematuria alone does not generally require any acute management, microhematuria outside of the context of a clearly documented infection warrants outpatient follow-up with the patient's primary care physician and/or urologist. This can be especially important as the rate of cancer diagnosis with microhematuria is 1–3% [2, 6]. Risk factors for malignancy are numerous but include symptomatic microhematuria, smoking status, degree of microhematuria, exposure to pelvic radiation or chemicals, and age [1, 2].

Gross Hematuria

Gross hematuria is visibly apparent to the patient and on examination of the urine. Nonetheless, gross hematuria may be intermittent, and a normal urinalysis, after symptoms have resolved, does not obviate a subsequent outpatient workup. Gross hematuria is likely urologic in origin with a cause identified in 50% of patients and a malignant etiology identified in 25% [3]. Although rare, a nephrologic cause should be considered in patients with red blood cell casts on microscopy, proteinuria, hypertension, and renal dysfunction [1].

The first step in assessing gross hematuria is to identify and manage any associated hemodynamic compromise because hemorrhagic shock can occasionally occur (see Fig. 31.1). Consideration should be given to an alternate etiology of hypotension as this is infrequent. Aggressive resuscitation should be undertaken in parallel with urgent urology consultation in the unstable patient as certain scenarios may necessitate immediate transfer straight to the operating room or interventional radiology suite.

The stable patient with gross hematuria should be assessed for urinary retention (see Fig. 31.1). Blood in the urinary tract will have a tendency to clot and obstruct the lower urinary tract or an indwelling urinary catheter. In this scenario, patients may endorse an inability to urinate, urinary urgency, a reduction in urine output, overflow incontinence, suprapubic pain, abdominal distension, or edema. Signs include generalized discomfort, a palpable painful bladder, visible voided blood clots or a clotted urinary catheter, edema, hypertension, and tachycardia.

The patient with suspected clot urinary retention should be catheterized emergently as long as there are no indications for urology consultation prior to catheter placement (see Fig. 31.1). Generally those with recent urinary tract surgery, trauma, or failed catheterization attempts should be catheterized only by a urologist due to the potential for further trauma to the urinary tract [7]. Patients should be catheterized in a private setting where vital signs can be measured, as a vagal response can sometimes result following bladder decompression [8]. In the setting of suspected clot retention, the initial catheter placed should be a 3-way catheter that has a large-caliber (22 Fr or 24 Fr). A 3-way catheter should be placed to facilitate continuous bladder irrigation with saline should this be required following bladder drainage and manual irrigation. A larger catheter (22 or 24 Fr) will allow for significantly improved evacuation of blood clots (initially with hand irrigation of the Foley) than the conventional first-line urinary catheter used in other situations (16 Fr) [9]. Special "hematuria catheters" are commercially available and may be stocked in the urology supply area of the operating room. If available, these catheters are ideal for this clinical situation, as they are large-bore 22- or 24-Fr 3-way catheters with a large opening at the tip for clot evacuation and are stiffer to prevent catheter collapse from aspiration. Initial placement of an appropriate catheter will permit efficient clearance of obstructive clots and minimize subsequent catheter changes. Lubricating the catheter well and use of 2% lidocaine gel intraurethrally can minimize discomfort in the placement of a larger catheter. If the patient is not in painful acute urinary retention, waiting for 10–20 min after injection of the gel prior to catheter placement is advised to allow for the lidocaine to take effect. A urologist should be involved following any concerns about catheterization failure such as ongoing symptoms, inability to advance the catheter to its hub, lack of drainage on catheter insertion, inability to irrigate a catheter, discomfort or excess resistance with irrigation, or Foley balloon inflation.

In the event that the patient presents with urinary retention and an obstructed catheter, the catheter should first be flushed with a cone-tipped (Toomey) syringe and sterile saline to relieve the obstruction. Ensure that a cone-tipped syringe is being used since a Luer-lock syringe does not have a tip diameter large enough to aspirate clots. The largest port on the catheter (center port in a 3-way catheter) should be used for irrigation and aspiration. After the bladder has started draining and discomfort is resolving, clot irrigation should be performed. If the catheter blocks and cannot be unobstructed by flushing, it may require replacement. Before removing the obstructed catheter, any anticipated challenges with replacing it should be carefully considered. Especially in the setting of recent urinary tract surgery, a urologist should generally be contacted before removal and/or replacement of the obstructed catheter.

After catheter placement and initial bladder decompression, further manual irrigation should be performed to evacuate the bladder of clots. If the catheter is draining, manual irrigation may be delayed to ensure that the bladder drains as much as possible, vagal response has not occurred, basic labs are sent, and any necessary imaging requests or consultations are in process. The catheter should be well lubricated prior to manual irrigation, as subtle motions during catheter manipulation can be uncomfortable. Manual irrigation is performed

through the middle (largest caliber) port of a 3-way catheter or the larger caliber port of a 2-way catheter. For both a 2-way and 3-way catheters, the Luer-lock port is used to inflate the balloon only. A 60 ml sterile syringe is filled with sterile saline and instilled slowly. In the case of a low-capacity bladder or a bladder filled with clot, the patient may not tolerate a full 60 cc and overfilling is suggested by increased resistance to fluid instillation or excessive patient discomfort. Overfilling the bladder can cause bladder trauma. After instillation, the syringe should be gently aspirated to draw back clot. Thick dense clot can sometimes require some force to aspirate, although care should be taken to ensure that one is not aspirating the bladder mucosa, which may be in contact with the catheter tip. If a regular (i.e., 16 Fr) catheter is in place and aspiration is not proceeding smoothly, a larger catheter should generally be placed if no contraindications to catheter exchange exist. If 60 ml of instillation is tolerated but limited clot returns on aspiration, a number of maneuvers can be attempted to completely irrigate the bladder. First, an additional 60 cc can be instilled into the bladder such that irrigation can now take place with 120 cc of fluid in the bladder. This additionally distends the bladder, reducing contact of bladder mucosa and the catheter eyelet. Rotating the catheter during irrigation, withdrawing or advancing the catheter, rapidly alternating a low-volume instillation aspiration, and deflating the balloon can also be helpful maneuvers to maximize clot irrigation. Clot irrigation can sometimes require 30–60 min and a reasonable attempt should be made to clear the bladder of clot prior to moving onwards.

Once the bladder has been completely evacuated of clots, consideration is given to continuous bladder irrigation (CBI) (see Fig. 31.1). CBI should not be used unless manual evacuation has ensured that large clots have been evacuated from the bladder. This is because these clots are unlikely to clear with CBI alone and may obstruct the catheter during passage. An obstructed catheter outflow with unattended continuous inflow in the setting of CBI can result in bladder trauma and recurrent symptoms of retention. CBI does not replace manual irrigation but can be useful to ensure that ongoing bleeding is efficiently evacuated from the bladder such that large clots will not form. Large bags of saline are connected to a cone-tipped tubing that will be attached to the small cone-tipped port of a 3-way catheter. Generally Y-tubing should be used to facilitate hanging two bags at once such that the need to exchange bags can be minimized. Only one bag should be unclamped and actively flowing at a time. The rate of continuous bladder irrigation can be varied by adjusting the tightness of a valve that will be present on CBI Y-tubing, which can constrict this tubing to reduce inflow. CBI rate is also dependent on the height of the irrigation bags above the bladder because irrigant flow is gravity dependent. Generally, CBI rate should ensure the urine is a dilute pink and can be slowed or stopped if the urine is clear. Red urine with clots should prompt the CBI rate to be increased.

The stable patient with an appropriately draining bladder is now assessed for the etiology of hematuria and appropriate disposition.

Generally, the stable gross hematuria patient without any clots should be fairly safe for discharge and timely outpatient workup. At least a urine culture should be obtained and a mechanism should be in place to follow-up culture results to ensure prompt antibiotic treatment in the event of a positive result. Those with urinary symptoms or features on urinalysis concerning for infection may be given empiric antibiotics for urinary organisms, which include gram-negative bacteria +/− enterococcus, and staphylococcus. Even with an empiric diagnosis of a urinary tract infection (UTI), it is still imperative that the patient be referred to a urologist for workup as this diagnosis is often revised when culture results return and an underlying malignancy may also be present. The risks and benefits of interrupting anticoagulation for co-existent conditions should be discussed and the prescribing physician notified. Patients on anticoagulation still require a full hematuria workup [1]. Patients can be counseled that their outpatient workup will generally include a detailed history and physical examination, repeat urinary testing, and additional workup such as a flexible cystoscopy under local anesthetic and upper tract imaging [1, 10]. Specific reasons to return to the ED include symptoms of worsening anemia, difficulties urinating due to urinary clots, and symptoms of worsening infection.

Even if a patient has presented in urinary retention from clots, they can sometimes still be discharged for an outpatient workup. Generally, this is in the setting of a limited resolved amount of bleeding that has resulted in clot-related obstruction but is now clear after catheter placement and limited manual and/or continuous bladder irrigation. Patients are generally discharged with an indwelling urethral catheter and short-term urological follow-up.

Patients with clot retention and significant acute renal insufficiency should be observed for possible post-obstructive diuresis (POD). POD can be life threatening and is discussed further in the section on urinary retention. It is very hard to estimate urine output in the patient on CBI, and POD monitoring will generally require additional clinical monitoring and serum electrolytes. Urologic consultation in this setting is advised.

The unstable patient or patient with persistent bleeding will require further inpatient assessment and management. After stability and urinary tract drainage are ensured, the initial steps of management include correcting any underlying coagulopathy and treating coexisting infection empirically. The source of bleeding in these patients should be determined. Sometimes the source of bleeding is readily apparent given the history or physical examination. Urology

consultation should then be obtained, as most sources of bleeding cannot be controlled in the ED. A discussion of selected oncologic etiologies is detailed below. If the source of bleeding is not readily apparent, differential diagnosis can broadly be categorized as upper or lower urinary tract. The best initial imaging test is a triphasic CT scan with noncontrast, early-contrast, and delayed-contrast images [10]. This test is sometimes called a CT urogram or CT intravenous pyeloureterogram. This will allow for an assessment of a variety of sources of bleeding in the upper and lower urinary tracts. Generally, most upper urinary tract causes can be excluded by imaging, while lower urinary tract etiologies are sometimes not readily apparent and findings within the bladder can be obscured by bladder clot. When a timely CT urogram is contraindicated (e.g., severe contrast allergy, renal failure, lack of availability, or an unstable patient), urology consultation is most appropriate to decide on the best initial imaging modality. Depending on the situation, this may include a renal ultrasound, MR urogram, noncontrast CT, or deferring upper tract imaging if a source is known [10].

Management of the specific source of bleeding will depend on its etiology. A discussion of selected oncologic etiologies of hematuria is detailed below.

Renal Mass

Although most renal masses are detected incidentally, a proportion will still present with hematuria, flank pain, nonspecific abdominal or back symptoms, or a palpable mass [11]. Generally, larger and more centrally located masses are more likely to cause hematuria. An antecedent history of trauma may have precipitated the hematuria but it usually occurs spontaneously. Hematuria associated with renal masses can be associated with ipsilateral flank pain, particularly if there is an ipsilateral perirenal hematoma or clot-related urinary obstruction. Paraneoplastic symptoms may also be present [12]. Most large renal cortical masses will be renal cell carcinoma [13], and masses involving the collecting system are likely to be urothelial carcinoma [14]. One should be wary of assuming that a small peripherally located renal mass or cyst is the cause for hematuria as these are common incidental findings. In some settings, an associated retroperitoneal hematoma may be of higher concern than the hematuria itself. A spontaneous retroperitoneal hematoma requires follow-up imaging, as sometimes the renal mass where the bleed originated is not initially visible amidst hematoma. In rare cases, spontaneous intra-tumor hemorrhage may cause significant pain or gross hematuria. Renal artery embolization can be considered after urologic consultation. Large renal masses should also prompt careful consideration of the presence of intraluminal renal vein or inferior vena cava tumor involvement, which can be present in up to 30% of patients undergoing radical nephrectomy [15] (Fig. 31.2). Vascular involvement may not be readily apparent if a noncontrast CT was obtained or if imaging identifying the mass is old. A further discussion of tumor thrombus is found later in this chapter.

Renal mass–related hematuria often requires intervention. In surgical candidates, this generally involves partial or radical nephrectomy or nephroureterectomy. A stable patient with limited hematuria may be discharged and have nephrectomy following a comprehensive outpatient workup. Significant ongoing hematuria may require a more timely nephrectomy. Nonsurgical candidates are often managed by angioembolization. In metastatic renal cell carcinoma or upper tract urothelial carcinoma, systemic therapy [16] and/or radiation [17] can also be of assistance in managing hematuria in nonsurgical candidates.

Ureteral Mass

Ureteral masses are often due to urothelial carcinoma [14]. A benign etiology such as a clot from hematuria originating in the ipsilateral kidney, papillary necrosis, or a radiolucent stone may mimic a ureteral mass. Hematuria associated with a ureteral mass is generally managed surgically. The degree of hematuria from a ureteral mass is usually limited and unlikely to require emergent intervention. Concomitant ipsilateral ureteral obstruction will often result in hydronephrosis. Obstructive uropathy and pain, renal dysfunction, or infection should be ruled out prior to outpatient assessment. Management of ureteral obstruction is discussed in more detail below.

Bladder Mass

Bladder masses diagnosed on imaging or prior cystoscopy are most commonly urothelial carcinoma [18]. Clot, mucosal folds, or debris in the bladder however can often mimic a bladder mass and accurate determination can be challenging radiologically. The patient with limited hematuria and a bladder mass is safe for outpatient urologic assessment. A urine culture should be sent to facilitate outpatient workup. A brief period of time until their assessment to await resolution of hematuria may actually be beneficial, as this will improve visualization during office flexible cystoscopy. For those with clot urinary retention, initial management is similar to undifferentiated hematuria as described above with manual followed by continuous bladder irrigation. The stable patient with timely resolution of their hematuria and a limited clot burden can be discharged for an outpatient assessment with an indwelling urethral catheter or following a trial of void. Ongoing hematuria or those with a significant clot burden

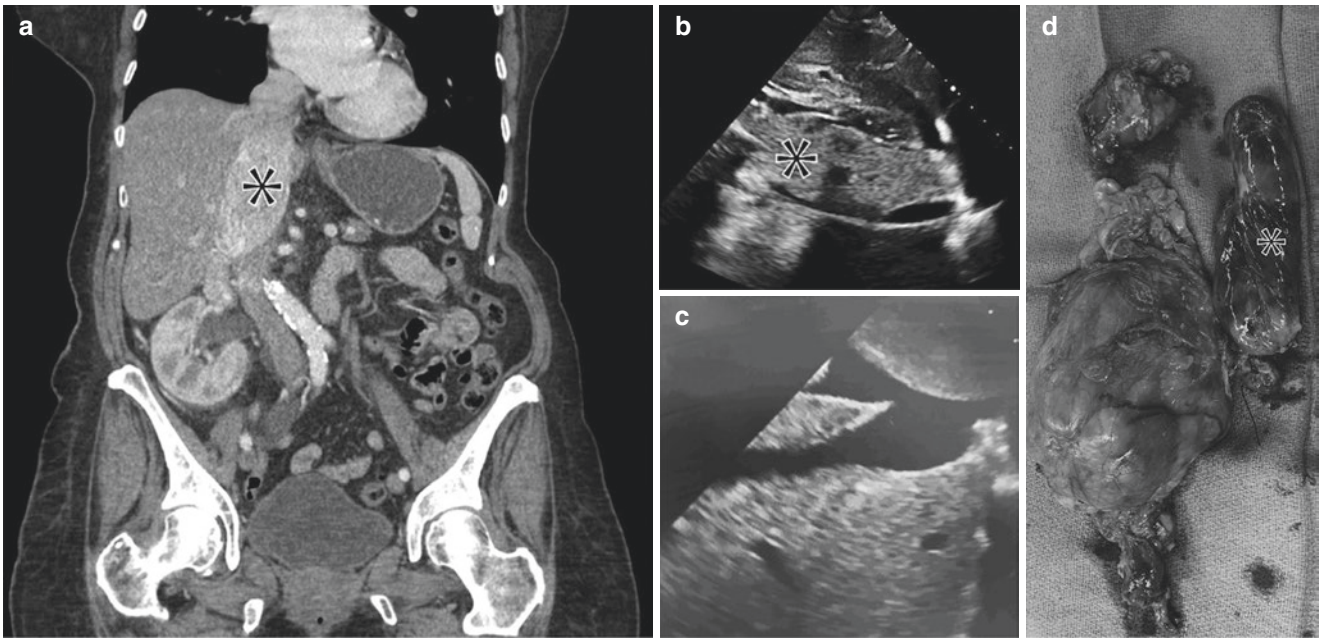

Fig. 31.2 Renal cell carcinoma with inferior vena cava tumor thrombus. A 71-year-old female presented to the ED with worsening back and abdominal pain, hematuria, and shortness of breath. She had a mild acute kidney injury along with normal liver function testing. She had an urgent CT pulmonary angiogram, which revealed no evidence of pulmonary embolus. (**a**) Abdominal CT scan revealed a large right renal mass (not pictured) along with a tumor thrombus in the inferior vena cava veins (*). (**b**) Echocardiography revealed that the tumor thrombus (*) extended to the level of the right atrium. (**c**) Echocardiography also revealed that the hepatic veins were free of tumor. Staging investigations were otherwise negative, and her severe symptoms prevented discharge. Because it was evident on CT that the inferior vena cava thrombus was comprised of tumor rather than bland thrombus, therapeutic anticoagulation was not initiated. She had a right radical nephrectomy and tumor thrombectomy with cardiopulmonary bypass shortly after admission. (**d**) The pathologic specimen from radical nephrectomy and tumor thrombectomy is pictured with a large right renal mass, adrenal gland, and tumor thrombus (*). Pathology revealed pT3c clear cell renal cell carcinoma with 0 of 33 lymph nodes involved. Expected long-term cancer-specific survival is above 50%

likely warrant inpatient urologic assessment. The management of a patient with suspected bladder mass on continuous bladder irrigation is usually to await resolution for a period of time followed by inpatient cystoscopy if resolution does not occur. Some patients with a bladder mass and very significant hematuria may be taken urgently to the operating room for cystoscopy under general anesthetic to evacuate the clots, control bleeding, and resect the bladder mass for diagnosis and staging. Patients with an advanced bladder mass and recalcitrant hematuria may require numerous interventions, including focused bladder radiotherapy.

Urethral Pathology

A variety of urethral pathology may present to the ED including tumors, strictures, trauma, and infections. Urethral pathology will present with bleeding, urinary symptoms, and a mass. Limited urethral bleeding will present as hematuria at the beginning of urinary stream, which resolves as the stream continues. Significant urethral bleeding will manifest as ongoing hemorrhage that continues outside of micturition if the source is distal to the urinary sphincter. Lower urinary tract obstruction may result in urinary retention or symptoms such as hesitancy, intermittency, slow stream, frequency, urgency, incomplete emptying, dysuria, post-void dribbling, and overflow incontinence.

For patients in urinary retention, the appropriate catheter placement technique will depend on the pathology. Urology should be involved prior to catheter attempts in patients with suspected external or iatrogenic urethral trauma to avoid worsening the degree of urethral trauma [7]. Often, these patients present with blood at the meatus or gross hematuria that clears during the void. In the patient with a suspected urethral stricture or bladder neck contracture after radical prostatectomy, a smaller (12–14 Fr) catheter should generally be used. Upfront cystoscopy for catheter placement may be required if initial gentle attempts fail and an inability to catheterize the urethra may require suprapubic tube placement.

Women in urinary retention may be especially difficult to catheterize when a urethral or vulvar lesion obscures the native urethral meatus or when prior perineal resection or radiation results in meatal retraction and/or stenosis. Lithotomy position, a speculum blade to retract the posterior vaginal wall posteriorly, additional lighting, and an assistant

to part the labia will help with difficult female catheterization. Some women may require a catheter be passed by palpation alone without visualization along the anterior vaginal wall when the urethral meatus is not visible. Additionally, ongoing bleeding and/or severe symptoms may require semi-urgent removal of a urethral lesion in women (e.g., strangulated urethral prolapse or caruncle).

Successful catheter placement in a patient with urethral pathology will often lead to clear urinary drainage because the eyelet of an appropriately placed catheter sits in the bladder, proximal to the site of a potentially bleeding urethral lesion. Ongoing urethral bleeding following catheter placement in a patient with urethral pathology may manifest as bleeding around the catheter. This bleeding may be controlled by gentle traction on the catheter along with compression of the distal urethra around the catheter for a period of time to allow for tamponade. This tamponade occurs when a closed system is created by the balloon of the Foley catheter on gentle traction at the bladder neck and the compressed urethra distally. In men requiring ongoing compression, gentle wrapping of the penis with a strip of gauze or Coban dressing can be helpful. A tourniquet effect resulting in penile ischemia and necrosis can result if the penile compression is overly restrictive, and so any dressing placed must be slightly loose and should be removed once the bleeding is controlled. Vigilant penile status monitoring is required if a penile tourniquet is used to avoid ischemic complications.

Once the acute presentation of a urethral lesion is managed, further evaluation will generally be handled as an outpatient. This workup includes a cystoscopy with a biopsy. Imaging for urethral pathology is best approached with MRI due to its enhanced soft-tissue resolution [19].

Urinary Retention

Urinary retention refers to an inability to empty the bladder appropriately. This is common in patients with cancer and may be an acute or chronic finding. The etiology of urinary retention may be an obstruction of the bladder outlet (i.e., the prostate or urethra) or from insufficient contraction of the bladder itself. The specific etiology for urinary retention is often multifactorial and both the bladder and outlet may play a role. Elucidating the factors contributing to urinary retention generally fall into the realm of outpatient urology.

Chronic urinary retention refers to a longstanding inability to empty the bladder. While this may manifest as recently worsening urinary symptoms, patients do not endorse an inability to void or acute pain. Chronic urinary retention is diagnosed by an elevated post-void residual. Post-void residual may be measured by portable bedside ultrasonography [20], but a variety of false positives exist for these machines including obesity, ascites, peritoneal dialysis, malignancy, and anatomic abnormalities such as bladder diverticuli and pregnancy. Post-void catheterization with measurement of the catheterized output is an alternative way to accurately measure post-void residual [20]. There is also no clear agreement on what is an abnormal post-void residual, but chronic urinary retention is often considered for PVRs above 300–400 ml [21]. Chronic urinary retention is generally assessed on a nonurgent outpatient basis unless an acute complication exists. Decompensation of chronic urinary retention may result in acute urinary retention, UTI, and renal failure. Generally, these issues are managed initially with urethral catheterization. Subsequent management is coordinated by urology and involves discharge and close follow-up in many cases.

Acute urinary retention refers to an acute inability to empty the bladder. Typically, patients have significant difficulty or total inability to void, pelvic pain, and overflow incontinence, which does not relieve their symptoms. They may have baseline urinary symptoms that have worsened recently including a weak stream, straining to void, incomplete emptying, hesitancy, intermittency, urgency, and frequent small volume voids. Those with a preceding or complicating infection may also have dysuria, fevers, flank pain, or testicular symptoms. Hematuria is a frequent presenting symptom for those with clot urinary retention. Signs include abnormal vital signs, a visually uncomfortable and restless patient, abdominal distension, and a palpable bladder. Other abnormalities on the genitourinary exam may be associated with the cause of the urinary retention. The emergency physician should have a low threshold to suspect acute urinary retention in any patient presenting with pelvic discomfort or urinary complaints.

A clinical diagnosis of acute urinary retention is usually confirmed by an elevated post-void residual measured by bedside ultrasonography [20]. If this is not immediately available, the patient should be catheterized empirically if acute urinary retention is suspected. A high volume of output upon catheter placement along with resolution of symptoms will confirm this diagnosis. Following catheter placement, the patient should be assessed for conditions associated with urinary retention including infection, hematuria, and renal failure. If isolated urinary retention is present and symptoms have resolved following catheter placement, the patient may be discharged with an indwelling urethral catheter for an outpatient workup and trial of voiding.

The amount of urine output following relief of urinary tract drainage is important. It is normal to have significant output upon initial relief of urinary tract obstruction (i.e., several hundred milliliters up to several liters in a short time period may be normal). If the urine output is less than expected, consideration should be given to an alternate diagnosis or to a mispositioned or obstructed catheter. Alternatively, a post-obstructive diuresis (POD) can result

following urinary tract drainage [22]. A patient is considered to have POD when they have a persistently high urine output (usually >200 mL/h) following relief of obstruction. This generally occurs following relief of obstruction in a patient with urinary retention that has resulted in renal failure. A similar phenomenon occurs following relief of bilateral ureteral obstruction or unilateral ureteral obstruction in a patient with a solitary kidney. A certain degree of POD is physiologic as longstanding obstruction and/or renal failure may have resulted in fluid retention requiring excretion following relief of obstruction. Pathologic POD may continue beyond this physiologic period resulting in fluid status and electrolyte abnormalities that may be life threatening.

Post-obstructive diuresis should be suspected in any patient presenting with retention and significant renal insufficiency. These patients should have urine output, volume status, vital signs, and electrolytes monitored following relief of their urinary tract obstruction. Patients without mental status changes should be provided free access to water, as thirst will allow them to self-regulate their fluid status. Aggressive fluid replacement should be avoided as this can prolong diuresis. The patient with limited polyuria, no electrolyte abnormalities, normal vital signs, normal volume status, and adequate mentation to drink when they are thirsty should be safe for discharge after a period of observation (e.g., 6 h). Patients not meeting these criteria will generally require admission for monitoring. In patients with a severe diuresis or who lack the ability to self-regulate their fluid status, fluid replacement is generally administered at a rate of half the urine output with 0.45% normal saline. Patients with severe renal failure, electrolyte abnormalities, or fluid status imbalance will benefit from nephrology consultation and modification of their fluid replacement based on urinary and/or serum electrolytes.

Hydronephrosis

Hydronephrosis refers to dilation of the collecting system of the kidney including the renal pelvis and calyces. This may be associated with ureteral dilation or hydroureter. The combination of renal and ureteral dilation is termed hydroureteronephrosis. The etiology of hydronephrosis may be obstructive or nonobstructive.

The first consideration in any patient with hydronephrosis is whether it may relate to urinary retention due to a lower urinary tract pathology. This will present with a distended bladder and bilateral hydroureteronephrosis. A urethral catheter will relieve lower urinary tract obstruction and should be placed expediently for patients with acute urinary retention, concern for infection, or renal failure. Concomitant bilateral ureteral obstruction may be present, and this should be considered in the patient with urinary retention and ongoing hydronephrosis, oliguria, signs of infection, or renal failure.

Although nonobstructive hydronephrosis may be relevant in certain populations, most hydronephrosis in the cancer population is obstructive. This is because ureteral obstruction by abdominopelvic malignancy is a fairly common complication of advanced malignancy [23]. The specific etiology of upper urinary tract obstruction may be intraluminal or extraluminal. Common intraluminal etiologies include ureteral tumors, stones, strictures, or an encrusted indwelling ureteral stent. External compression may result from any number of different intraabdominal pathologies. Malignant etiologies such as retroperitoneal or pelvic lymphadenopathy or a pelvic mass are fairly common [23]. Otherwise, ureteral obstruction may be iatrogenic, post-traumatic, inflammatory, infectious, congenital, or idiopathic. Although the differential diagnosis of ureteral obstruction is lengthy, the main consideration for the emergency physician can be simplified into whether urgent decompression is required or not.

It is also important to understand that urinary tract obstruction may also be present without significant hydronephrosis [24]. This is particularly true in the setting of acute obstruction when hydronephrosis may not have had a chance to develop. Accordingly, the patient with a clinical history suggestive of obstruction, even with limited or absent hydronephrosis, should be evaluated by a urologist (e.g., the patient with anuria despite urethral catheterization and radiographically evident pathology that may cause ureteral obstruction on CT). Moreover, changes in the extent of hydronephrosis between interval studies is difficult to quantify and interpret and can vary based on numerous factors other than the degree of obstruction [25].

The indications for urgent upper urinary tract decompression are a concern for obstructed UTI, renal failure, and uncontrolled flank pain. The emergency physician should have a low threshold to suspect infection in a patient with hydronephrosis and signs of sepsis or a positive urinalysis. The urinalysis may be falsely negative as a complete obstruction may disconnect the obstructed urinary tract from voided urine. Given the gravity of missing an obstructed UTI, the threshold should be low to consult urology in the setting of hydronephrosis with a concern for infection. Significant recent worsening of renal insufficiency, particularly with associated oliguria, should also be considered an indication for urgent decompression. It is sometimes challenging to elucidate whether a minor degree of acute kidney injury relates to limited hydronephrosis in the acute setting. When in doubt, a urology consultation is reasonable, but consultants may elect to observe this hydronephrosis in the stable patient and trend their renal function. Ongoing symptoms despite analgesia are also an indication for upper urinary tract decompression.

Upper urinary tract drainage is accomplished by ureteral stenting or nephrostomy tube placement. In the infected patient, randomized data have not supported any difference in meaningful outcome such as time to fever resolution [26]. Ultimately, the decision on which to perform is very nuanced and dependent on patient factors. In the patient requiring urgent intervention, the best measure will depend on what is available first. It is known that there is significant regional variation in stent versus nephrostomy tube placement likely for this reason [27]. Contraindications to each decompression method are first assessed. Nephrostomy tubes will generally be contraindicated in those with coagulopathy and may be more difficult in the patient who cannot be placed prone, has morbid obesity, or lacks hydronephrosis. Ureteral stents will not be feasible in the patient who does not have easy endoscopic access to the ureter—in the oncologic setting this is due to trigonal invasion of a large pelvic mass or due to prior lower urinary tract surgery. Additionally, suspicion of longstanding complete obstruction will be very difficult to bypass with a ureteral stent and consideration should initially be made for nephrostomy tube placement. While a ureteral stent can be placed under local anesthetic, it is often painful and usually performed with sedation or a general anesthetic. Anesthetic requirements are likely less for nephrostomy tube placement and this procedure can be conducted at the bedside in an emergency if necessary.

If no specific factors indicate one procedure over the other, the choice for nephrostomy tube versus ureteral stent is generally undertaken by shared decision-making. Ultimately, patient and practitioner factors heavily influence the choice of urinary diversion modality [28].

Following decompression of the upper urinary tract by either stent or nephrostomy tube, it is important to consider the possibility of post-obstructive diuresis. This will generally occur in the setting of significant renal insufficiency associated with the relieved obstruction. This is discussed further in the setting on urinary retention.

One particular etiology of obstruction that warrants discussion in the oncologic patient is stent failure. Abdominal malignancies often cause ureteral compression requiring ureteral stent placement. Due to progressive growth of these malignancies or encrustration of an indwelling stent over time, recurrent obstruction can develop despite an indwelling stent. The diagnosis of stent failure can be hard to assess in the ED as degree of hydronephrosis is not necessarily indicative of impaired drainage. Generally, stent obstruction should be suspected if the patient has recurrent clinical sequelae of obstruction. One should look for signs of obstructed infection, renal dysfunction, worsening hydronephrosis, and acute or subacute worsening of flank pain. This diagnosis of stent obstruction can sometimes be difficult to make as indwelling stents or the underlying obstructive pathology may cause urinary symptoms or flank discomfort. Theoretically, renography could assist in the diagnosis, but it is often not necessary. Management is generally either with a stent exchange or conversion to nephrostomy tube with subsequent stent removal. The latter approach is warranted particularly if re-obstruction occurs quickly, a stent is poorly tolerated, or stent exchange is complicated.

Although nonobstructive hydronephrosis is possible, this is a difficult initial diagnosis to make in the ED. The diagnosis generally requires diuretic nuclear renography to rule out obstruction. Nonetheless, nonobstructive hydronephrosis may be evident from the history, particularly if diuretic renography has previously demonstrated a lack of obstruction. Possible nonobstructive etiologies include vesicoureteral reflux, pregnancy, excessive hydration, congenital anomalies, and prior corrected obstruction. A parapelvic renal cyst may also often masquerade as hydronephrosis [24]. Patients with history of radical cystectomy with urinary diversion can have physiologic hydronephrosis without obstruction and a loopogram or pouchogram will be diagnostic. Because of the relative infrequency of nonobstructive hydronephrosis and the difficulty in making this diagnosis, it would be reasonable to consider most new hydronephrosis in the ED as obstructive.

Testicular Cancer

Testicular cancer is the most common solid organ malignancy in men aged 15–44 years [29]. As men in this age group infrequently see a healthcare practitioner in the outpatient setting, they often have delayed diagnosis [30–32] and may present symptomatically to the ED. Presenting symptoms include a testicular mass, enlargement, and discomfort (Fig. 31.3). They may also have symptoms of systemic disease including abdominal or back pain, respiratory symptoms or hemoptysis, breast enlargement or tenderness, or neurologic symptoms [33]. The physical exam will usually reveal a palpable testicular mass with ipsilateral hemiscrotal enlargement. A reactive hydrocele, discomfort, contralateral or multifocal masses are also sometimes present. The genitourinary examination is often otherwise unremarkable. An abdominal mass may be present in the setting of bulky retroperitoneal adenopathy. Gynecomastia may also be present in the setting of elevated tumor markers or a testicular stromal tumor. The respiratory exam may be abnormal due to thoracic metastases. A Virchow's node (supraclavicular) may be palpable along with additional neck adenopathy. Patients will rarely also have symptoms from brain metastases, bone metastases, venous obstruction, or thromboembolism [34]. The differential diagnosis for testicular masses includes epididymoorchitis with possible abscess formation, testicular torsion, hernias, paratesticular lesions, hydroceles, varicocele, inflammatory conditions, and trauma. Various other

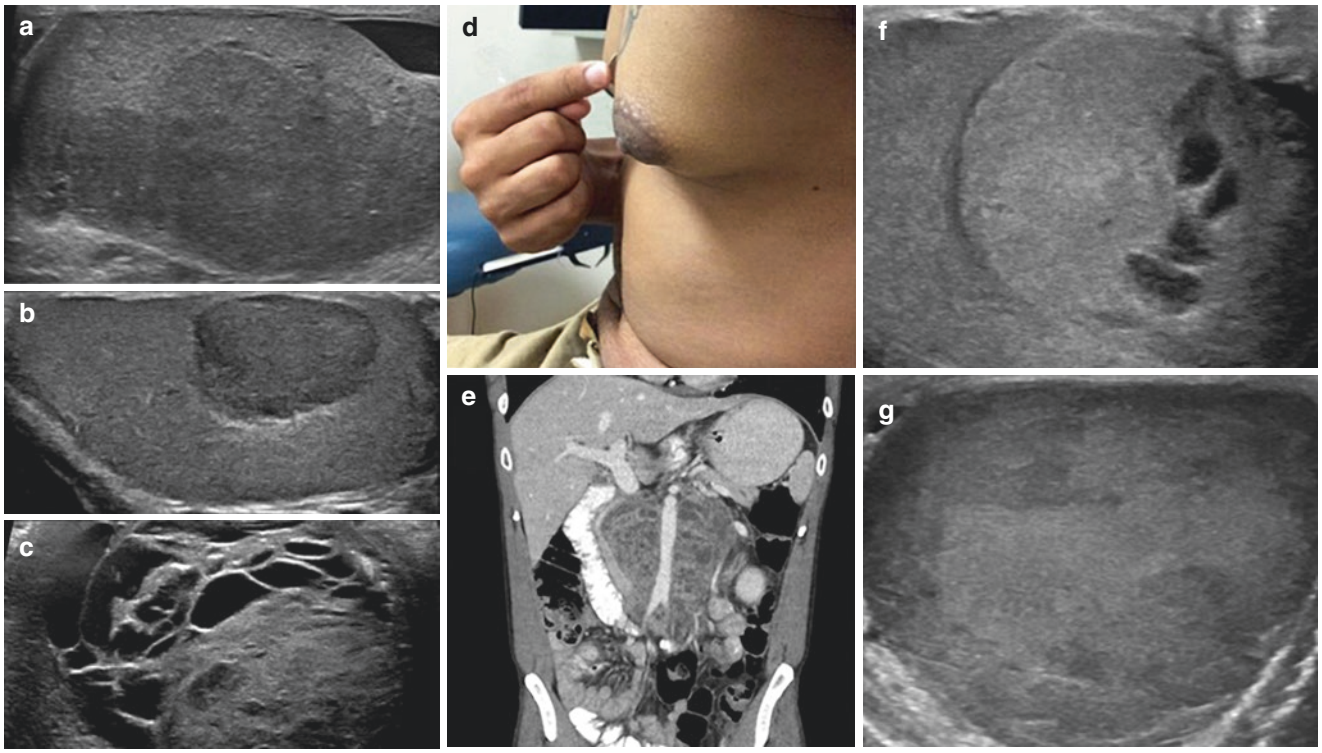

Fig. 31.3 Testicular tumors. These patients presented initially with scrotal complaints, were imaged with a scrotal ultrasound, and ultimately underwent radical orchiectomy. (**a**) This poorly circumscribed hypoechoic mass was found to be lymphoma. (**b**) This well-circumscribed, small, and difficult-to-palpate lesion was found to be a Leydig cell tumor. (**c**) Some testicular tumors have significant hypoechoic areas consistent with cystic components—this finding is suggestive of teratoma, which comprised the majority of this patient's nonsemonimatous germ cell tumor. (**d**) Gynecomastia is sometimes associated with testicular tumors. This can occur due to hormonal secretion from testicular stromal tumors (in this patient estradiol was being secreted by the Leydig cell tumor depicted in **b**). Gynecomastia can also occur due to elevated beta-HCG secreted by germ cell tumors. (**e**) This patient had increasing abdominal pain and leg swelling during chemotherapy for nonseminomatous germ cell tumor. He had multiple presentations to the ED for pain control. He was eventually diagnosed with growing teratoma syndrome as his large retroperitoneal mass was expanding during chemotherapy. This mass also compressed and laterally displaced the inferior vena cava. The diagnosis of growing teratoma syndrome should be suspected in the patient presenting with worsening symptoms during chemotherapy for nonseminomatous germ cell tumor. Imaging will reveal progressive growth of metastatic disease from pre-chemotherapy scans. In this patient, chemotherapy was interrupted and the patient was taken for surgical resection. Pathologic findings from surgery revealed pure teratoma. (**f**, **g**) Germ cell tumors can be hypo-, iso-, or hyperechoic, and can sometimes be difficult to distinguish from surrounding normal parenchyma

malignancies or conditions can cause the systemic findings detailed above. Although the differential diagnosis is broad, testicular cancer should always be considered for any scrotal complaint in the young man.

Initial workup for a testicular complaint should include scrotal ultrasonography to confirm the presence of a testicular mass with a urinalysis to rule out infection [35] (see Fig. 31.3). The mass will generally appear as a circumscribed hypoechoic hypervascular lesion on sonography that is within the testicle itself. The presence of blood flow on Doppler sonography will assist in ruling out testicular torsion, although cases of torsion may be present with vascularity. Although these findings are characteristic, testicular cancer can sometimes be present without visible flow on Doppler or a visible mass [35]. A negative urinalysis will generally rule out an infectious etiology, but additional sexually transmitted infection testing may be indicated in certain scenarios. Complete blood counts, a complete metabolic panel, and testicular tumor markers (alpha-fetoprotein [AFP], beta-human choriogonadotropin [beta-HCG], and lactate dehydrogenase [LDH]) should also be sent. Generally a high AFP (>20 ng/mL) or beta-HCG along with a characteristic testicular mass will strongly suggest the diagnosis of testicular cancer. Those with extra-testicular signs or symptoms warrant emergent imaging with a CT scan of the chest, abdomen, and pelvis. Extremity complaints or concern for pulmonary embolism should also prompt extremity duplex and/or CT pulmonary angiography. Neurologic complaints or a very elevated beta-HCG (>5000 IU/mL [36]) warrant brain imaging or spine imaging with MRI. Patients with an equivocal diagnosis or without any extra-testicular complaints can have staging imaging deferred to the outpatient

setting where it may be omitted if they are diagnosed with a benign lesion. Alternatively, a chest X-ray rather than CT may be sufficient in staging patients with suspected stage I seminoma [35].

If the patient has systemic symptoms or significant metastatic disease burden, a conversation with a urologic oncologist or genitourinary medical oncologist prior to discharge is warranted. In this uncommon scenario, urgent inpatient treatment is sometimes required and may be undertaken based on a presumptive diagnosis from the clinical scenario and serum tumor markers even without a formal tissue diagnosis [36]. It is more common that a new testicular cancer patient will be assessed as an outpatient with close interval follow-up with a urologist. In general, biopsy of retroperitoneal lymph nodes is not pursued and a prompt radical orchiectomy is sufficient for diagnosis.

Retroperitoneal Mass with Venous Involvement

Renal cell carcinoma is associated with venous involvement in 30% of patients undergoing radical nephrectomy [15]. Other retroperitoneal tumors, including adrenal, upper tract urothelial, sarcoma, and testicular cancers can also involve the venous system. The level of venous involvement can range from thrombus within the small intrarenal vessels alone to complete involvement of the renal veins, inferior vena cava, and right atrium. Patients are often symptomatic, and the degree and pattern of morbidity will depend on their level of venous involvement (see Fig. 31.2). One should have a high degree of suspicion for venous involvement in the patient with a known or suspected renal mass presenting with worsening symptoms. Symptoms can include hematuria, lower extremity edema, ascites, abdominal flank or back pain [11], and a variety of other symptoms associated with generalized malignancy, renal failure, hepatic failure, or cardiac failure. Physical exam and lab findings are variable and will also associate with degree of impact on various organs. The diagnosis of venous involvement is generally made by CT scan with IV contrast. Pulmonary embolism should be ruled out with a CT pulmonary angiogram in any patient presenting with respiratory symptoms. Budd-Chiari syndrome must be considered in the patient presenting with a thrombus close to the hepatic veins [37]. An echocardiogram will be helpful in assessing the patient with intra-atrial thrombus and evidence of heart failure. Ultimately, urologic oncologic consultation should be obtained to develop a plan for the patient prior to considering discharge. Anticoagulation is not necessarily indicated if venous involvement relates to tumor thrombus rather than bland thrombus and should be started as a shared decision with urologic oncologic [38]. Particularly in the case of intracardiac thrombus, use of heparin should be discussed with urologic oncologic prior to initiation because the development of heparin-induced thrombocytopenia may prevent safe cardiopulmonary bypass [39].

The first consideration for a patient with a venous tumor thrombus is whether they are a surgical candidate for tumor thrombectomy and the timeline in which this operation needs to occur (see Fig. 31.2). Depending on the primary malignancy and degree of symptoms, these patients may be admitted for symptom control, workup, and timely inpatient intervention. This is a complex problem, and some patients may not be candidates for surgery due to patient or malignancy-related factors. In these situations, systemic therapy can sometimes be effective [40].

Penile Cancer

Penile cancer is rare with 2200 cases a year in the United States [41]. Nonetheless, the delayed presentation of this cancer is well documented [42, 43]. It is essential that this diagnosis be considered in any patient presenting with a penile lesion (Fig. 31.4). Clinical presentations can range from a subtle asymptomatic erythematous plaque that may be associated with carcinoma in situ to a large fungating penile mass causing urethral obstruction. Patients with a "rash" of the genitals are frequently treated with antifungals and steroids for a prolonged period prior to delayed diagnosis of penile cancer [42]. Additionally, one should also have a low suspicion for the patient with a condyloma to have penile cancer as the enlarging verrucous lesion is also a fairly common presentation and penile cancer is associated with HPV in 40% [44]. When in doubt, urology or dermatology consultation should be obtained. A patient with a penile mass involving the urethra may sometimes present with urinary retention or significant urinary symptoms. Urethral catheterization can be attempted, but the meatus may not be visible amidst a large mass on the glans penis. In some situations, this will require suprapubic catheterization by urology or interventional radiology. Patients with penile cancer may also present with superinfection of a necrotic penile mass, including Fournier's gangrene, albeit an infrequent situation.

Another acute presentation associated with penile cancer is inguinal adenopathy. The first site of metastasis from penile cancer is to the inguinal lymph nodes [45]. These are generally palpable when they are involved in the nonobese patient (see Fig. 31.4). There are also some situations of bulky inguinal adenopathy without a diagnosed primary, which may ultimately lead to a diagnosis of anal, urethral, vulvar, or lower extremity cancers that drain into these nodal basins. The patient with asymptomatic inguinal adenopathy is likely safe for an outpatient assessment. However, in some situa-

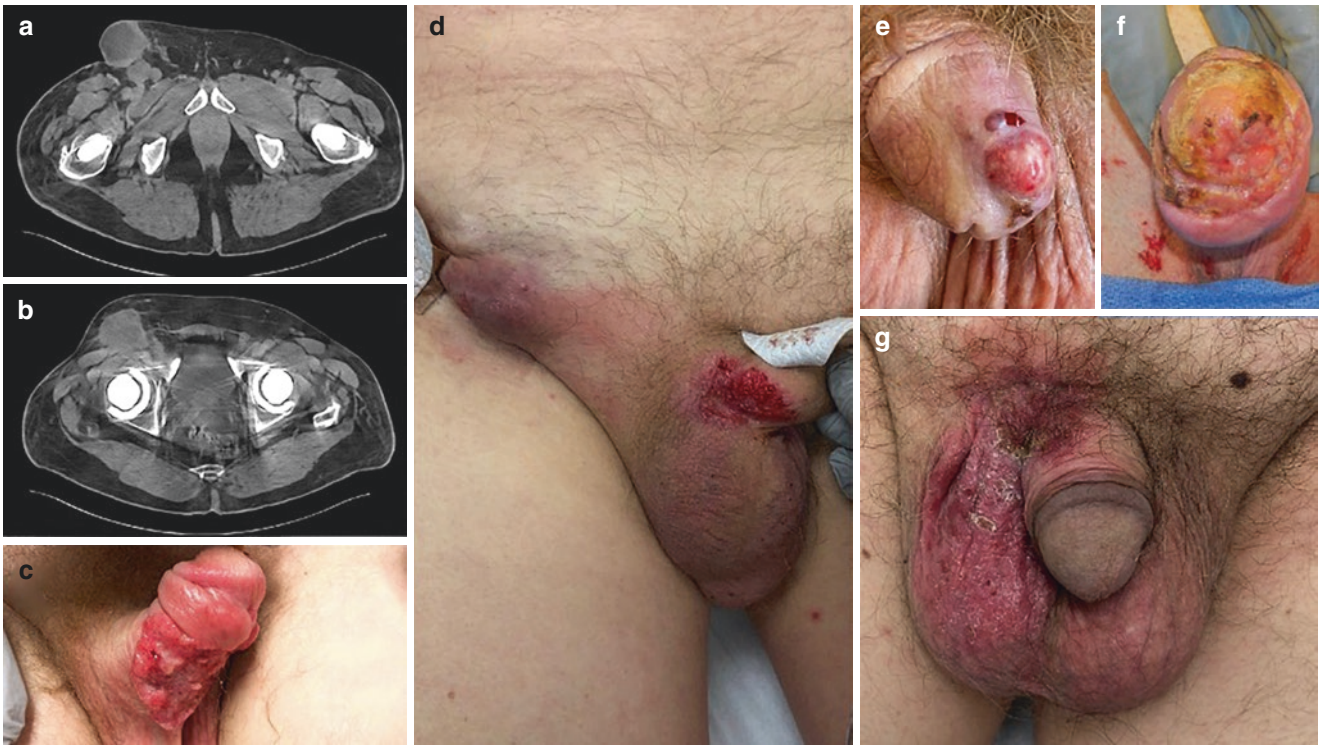

Fig. 31.4 Penile cancer. (**a**, **b**) Inguinal adenopathy associated with penile cancer can lead to various complications. In (**a**) a necrotic lymph node has eroded through the skin and resulted in a nonhealing wound and ongoing purulent discharge. Bulky inguinal adenopathy can also erode into the femoral vessels. In (**b**) there is no separation between the bulky right inguinal lymph node and either the femoral artery or vein. This can eventually result in life-threatening hemorrhage. (**c**) Sometimes a penile mass is not immediately evident as in this patient with penile squamous cell carcinoma who did not look at the ventral aspect of his penis in several years. (**d**) Penile cancers can also be limited in size relative to associated adenopathy. Here a small squamous cell carcinoma is seen on the penile shaft. Bulky inguinal adenopathy is evident on exam. This patient's pelvic CT scan is depicted in panels (**a**), (**b**), and (**e**). Cancers can rarely metastasize to the penis as in this patient with renal cell carcinoma involving the glans penis. (**f**, **g**) Penile cancers may initially be confused for a benign process. The patient in (**f**) had a circumcision for what was thought to be chronic balanitis. The pathology from this circumcision revealed squamous cell carcinoma. He then needed a partial penectomy and inguinal lymph node dissection. This patient in (**g**) was treated with steroids for months due to a penoscrotal rash. Progression of the lesion prompted a biopsy revealing extramammary Paget's disease. He required excision of all the superficial tissues of his penis and scrotum

tions inguinal adenopathy may erode into the femoral vessels, which can cause massive hemorrhage [46, 47]. Urgent urologic oncologic and vascular surgery consultation should be obtained in this case. Additionally, patients with inguinal adenopathy present with severe leg, perineal, or penoscrotal lymphedema, with pain and skin changes. Superimposed infection and deep vein thrombosis are important to rule out. Primary cancer treatment along with symptom control, palliative care consultation, and lymphedema clinic referral can all be useful.

Prostate Cancer

Prostate cancer is the most common cancer in American men with 174,650 cases in 2019 [48]. Although many prostate cancers are localized, metastatic disease is still a large cause of morbidity, and it is the second most common cause of cancer death in America with 31,620 deaths in 2019 [48]. Generally, prostate cancer can present to the ED in three ways.

(i) Urinary retention and/or hematuria. The ED management of these conditions is addressed above. Patients should be referred to a urologist for further management.
(ii) Upper urinary tract obstruction is also common in advanced prostate cancer. This is also discussed above. Patients should be referred to a urologist for further management.
(iii) Spinal cord compression. Prostate cancer is the second most common etiology of malignant spinal cord compression [49]. Those with bony metastatic disease can experience bony pain, pathologic fracture, and spinal cord compression. Patients with cord compression require timely management to minimize permanent

neurologic sequelae [50]. The crucial difference in managing prostate cancer cord compression compared to other cancer sites is the need to institute androgen deprivation therapy. It has been known since the 1940s that prostate cancer is sensitive to the lowering of serum testosterone, which induces atrophy in prostate cancer cells [51]. In the setting of cord compression, a tissue diagnosis of prostate cancer is not required to institute androgen deprivation therapy. Nonetheless some clear evidence of prostate cancer should be present such as a significantly elevated PSA, osteoblastic metastases, and an abnormal rectal examination. Rapid reduction of testosterone is essential in the setting of cord compression. The conventional method of doing this in the outpatient setting is to start the patient on an androgen receptor blocker (e.g., bicalutamide) along with delayed administration of GnRH agonist. This is not appropriate in suspected cord compression because these methods take a long time to work and may induce a testosterone flare [52]. Instead patients must be started on either a GnRH antagonist [52], ketoconazole, or have an urgent bilateral orchiectomy. Other than androgen deprivation therapy, management of prostate cancer cord compression has the same basic principles as other cancer types, including complete spine imaging, high-dose steroids, and early involvement of spine surgery and radiation oncologic consultants. The prostate cancer patient can sometimes present with spinal cord compression after having received multiple prior lines of systemic therapy with progression of disease. Testosterone is generally already castrate in this situation and androgen manipulation will have little effect.

Postoperative Issues

Prostatectomy

Catheter or Urinary Issues Following prostatectomy, patients will be discharged with a urethral catheter as the vesicourethral anastomosis heals. Patients may present with decreased urine output, catheter discomfort, catheter bypassing, hematuria, or debris in the catheter. Usually the only intervention that should be undertaken in the ED is to consider gently irrigating or flushing the catheter. The catheter should generally not be removed, repositioned, or replaced by anyone other than a urologist because of the recent anastomosis and the potential that this has already disrupted or may potentially be disrupted by catheter manipulation. At times, patients will present with urinary retention or new urinary symptoms following prostatectomy catheter removal. Urinary retention and a UTI should be ruled out. Generally, patients should not have a urethral catheter inserted unless the issue is discussed with a urologist due to a concern for traumatizing a recent vesicourethral anastomosis. Catheter bypassing and urinary incontinence after prostatectomy catheter removal are normal, and patients should be reassured, provided it is clear that their bladder is empty and they are not retaining urine.

Pelvic Collections Pelvic collections are commonly found in the patient presenting post-prostatectomy who might receive a CT scan for a variety of indications. The differential diagnosis includes lymphocele, abscess, urinoma, seroma, hematoma, or bowel injury. Radiologic characterization is often not possible, and these collections may frequently be described as abscesses because they contain gas, although this appearance can relate to hemostatic products used at the time of surgery (e.g., oxidized cellulose) [53]. Patients with signs or symptoms of an infection require prompt antibiotic treatment, resuscitation, and percutaneous drainage. Those with bleeding, urinoma, or findings concerning for bowel injury require additional procedures. Generally urologic consultation should be obtained following the initial management of a patient with a pelvic collection post-prostatectomy.

Radical Cystectomy

The readmission rate after radical cystectomy (RC) for bladder cancer is 20–30%; thus, these patients are frequently seen in the ED after undergoing surgery [54].

Fever

Fever is one of the most common reasons for readmission after RC as infectious concerns comprise 25% of postoperative complications [54]. The patient with a fever after RC should be worked up broadly. Specific etiologies include pyelonephritis, intraabdominal infections, wound infections, urinary leak, bowel leak or bowel injury, pulmonary embolism or pneumonia, *Clostridioides difficile* colitis, and line sepsis. Broad workup including chest imaging and abdominal imaging are warranted. Due to bowel being routinely used as part of the urinary diversion, urinalysis and culture may be falsely positive and not indicative of the true source of infection. Patients will often have received multiple antibiotics recently around the time of surgery and prior readmissions; thus, consideration should be given to coverage of MRSA and ESBL in the choice of empiric antibiotic. CT scan of the abdomen and pelvis is essential in the early postoperative period. Timely urologic consultation is advised.

Hydronephrosis

Hydronephrosis is a common finding on a CT scan performed in the patient after RC. The approach to these patients is similar to the general approach detailed above. Strong consideration should be given to prompt nephrostomy placement in the patient presenting with sepsis or renal failure. Retrograde attempts at stent placement are not usually possible.

Urinary Tract Infection

UTIs after RC are relatively common. Symptoms include fever, chills, and flank pain. Presentation can be insidious in the patient presenting with lethargy and mental status changes. Early antibiotic treatment and resuscitation is essential. Urinalysis and culture can both be misleading as this will usually be positive in a patient with a urinary diversion even in the absence of UTI. The urinary findings will have to be correlated with the clinical picture to make a diagnosis, and urology consultation can be helpful in making this determination. Concern for UTI should prompt abdominal imaging, and hydronephrosis generally requires nephrostomy placement. Although hydronephrosis may sometimes be physiologic in the patient with a urinary diversion, the consequences of missing this source of infection in an obstructed UTI is usually an indication for nephrostomy.

Dehydration

Gastrointestinal issues are the most common complication after RC and associated dehydration is common [54]. Patients will present with malaise, fatigue, reduced appetite and oral intake, diarrhea, nausea, vomiting, and reduced urine output. Labs will often reveal an increased creatinine and electrolyte abnormalities. Intraabdominal pathology should be ruled out; the diagnosis of dehydration is one of exclusion. Patients presenting with dehydration will often require admission for rehydration and closer monitoring on discharge to avoid another readmission. Associated gastrointestinal issues should be managed by the surgical team.

Leg Swelling

In addition to the usual differential, the emergency practitioner should be especially suspicious of deep vein thromboses due to a high rate of venous thromboembolism after RC [55]. Additional etiologies include postoperative fluid overload, pelvic fluid collection, and lymphedema related to a pelvic lymph node dissection.

Diarrhea

Diarrhea can be a challenge after RC due to bile acid malabsorption from use of the terminal ileum as part of most forms of urinary diversion. The ileocecal valve may also not be present in the patient with an Indiana pouch. Diarrhea should be differentiated from tenesmus or pelvic discomfort, which can often be secondary to intraabdominal pathology. Nonetheless, patients are at risk of infectious etiologies including *Clostridioides difficile* colitis. Patients presenting with diarrhea should be resuscitated, and infection with dehydration and electrolyte abnormalities ruled out. Antidiarrheals such as loperamide or cholestyramine can be used once infection is ruled out.

Acute Abdomen

Patients presenting with an acute abdomen are managed similarly to other surgical patients. Early surgical consultation is obviously warranted. Etiologies could relate to the gastrointestinal or urinary system and the differential diagnosis is complex [54]. Patients should be resuscitated and if imaging is performed before urologic consultation, a CT urogram is often more useful than a standard CT scan because this will aid in differentiating many complications associated with the urinary diversion. Oral contrast and/or rectal contrast may also be useful depending on the situation.

Stomal Complications

Most patients will have an ileal conduit after RC. Patients may develop various issues with these conduits, including pouch leakage, parastomal hernias, parastomal dermatitis or infections, or issues with the stoma itself (e.g., bleeding, varices, stenosis, prolapse, and necrosis). Stomal bag-related issues and parastomal dermatitis are often best handled by involving a wound ostomy continence nurse to help with troubleshooting and finding the best ostomy supplies. Stomal stenosis will present with a distended conduit on imaging along with oliguria and renal dysfunction; management is generally by stomal catheterization and surgical consultation is advised. Patients with portal hypertension may present with stomal varices, and management is similar to varices elsewhere in the gastrointestinal tract. Blood loss anemia is common in this clinical context. Parastomal hernias are very common on imaging, present in 50% of patients [56]. Although parastomal hernias may be dramatic on the physical examination, these are generally not an acute issue in the ED unless hernia-related complications develop. If there is concern for obstruction or strangulation associated with a parastomal hernia, early surgical consultation is advised.

Continent Diversion Problems

Continent urinary diversion includes both continent cutaneous diversions and orthotopic neobladders. Many types exist and the exact configuration of the urinary diversion is often unclear to the emergency physician. Patients with continent cutaneous diversions will have some form of catheterizable abdominal stoma, while those with an orthotopic neobladder will void per urethra. Various issues with these complicated urinary diversions will cause patients to present to the ED. The emergency provider should seek urologic consultation in devising the management plan and always keep urinary retention or diversion rupture within the differential diagnosis. Generally, procedural interventions should be avoided by the nonspecialist as the anatomy of the urinary diversion is often unfamiliar.

Nephrectomy

Hematuria

Patients presenting after partial nephrectomy with hematuria may develop a pseudoaneurysm or arteriovenous fistula [57]. These patients can present with hemorrhagic shock. In the stable patient, initial resuscitation should be commenced and a pseudoaneurysm/AVM ruled out with CT angiography. In the unstable patient, urologic consultation should be obtained immediately. Management should be coordinated with urology and will often involve selective angioembolization by interventional radiology [58]. Patients should not have hematuria after radical nephrectomy and thus should be assessed as any other patient presenting with hematuria.

Abdominal Collections

Patients after partial or radical nephrectomy may frequently receive a CT scan for abdominal complaints revealing an abdominal fluid collection. The differential diagnosis includes abscess, urinoma, seroma, hematoma, pancreatic leak, bowel injury, or biloma. Generally, initial management includes stabilization with empiric antibiotics if signs of infection are present. The patient should receive nothing by mouth and urologic consultation should be obtained to assess for management of the collection. Many postoperative collections are incidental and asymptomatic but occasionally percutaneous drainage by interventional radiology is required. The rare situation of an acute abdomen suggestive of peritonitis or bleed may warrant an exploratory laparotomy.

Pulmonary Symptoms

The common nonsurgical causes should be ruled out including pulmonary embolism, heart failure, myocardial infarction, and pneumonia. Nephrectomy-specific etiologies can include a pneumothorax, pneumomediastinum, or pneupericardium, which can result from diaphragmatic entry [59], diaphragmatic neuromuscular pathology [60], or difficulty with inspiration due to a nephrectomy bed collection or incisional pain.

Conclusion

Urologic oncologic emergencies present frequently to the ED. Knowledge of urologic anatomy and common presenting issues aids greatly in the triage and initial management of these patients. Most acute presentations will relate to bleeding, obstruction, or infection of the urinary tract. A thorough history and physical exam with pertinent laboratory studies will clarify the presenting complaint, but imaging is frequently essential in diagnosis. Initial management focuses on stabilizing the patient, controlling pain, and ensuring appropriate urinary tract drainage. Early coordination with urologic consultants can be helpful to ensure that appropriate steps are taken in a timely fashion. Once the acute situation has been managed, a full assessment is nuanced and usually best performed in the outpatient setting by a specialist. When an outpatient assessment is appropriate, timely coordination of an appointment is essential to ensure optimal patient care and avoiding repeated ED presentation.

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Gynecology

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Case Study 1

A 63-year-old woman with stage IIIC high-grade undifferentiated ovarian cancer underwent extensive surgery followed by chemotherapy. However, the disease rapidly progressed and the course was complicated by ureteral obstruction that was relieved by bilateral percutaneous nephrostomy tubes, and deep venous thrombosis.

After the fifth cycle of carboplatin and Taxol, she presented to the emergency department with several days of worsening abdominal pain, distension, and nausea, and was found to be neutropenic with lactate level of 8. CT scan showed high-grade small bowel obstruction, closed loop in nature. The distal point was associated with a segment of edematous bowel, normal in caliber. A differential diagnosis of bowel obstruction due to malignancy or adhesions, and possible bowel ischemia seen on CT as edema, was made. Overall, the tumor disease burden seemed to have improved with no new disease sites.

The dilemma of emergent surgery for bowel obstruction and possible bowel ischemia and high mortality rate versus *conservative management in the setting of progressive disease with a poor prognosis was discussed with the patient. A decision was made to proceed with surgery. During exploratory surgery, two distinct adhesive lesions that were tethering the bowel to the base of mesentery were found. They were lysed and the area of closed loop was released. There was no extensive disease in the abdomen, and only few 5 mm areas of tumor implants, ablated by chemotherapy, were at the small bowel mesentery. This case illustrates the management dilemma frequently faced in the cases of bowel obstruction in patients with pelvic malignancies.*

Case Study 2

An 80-year-old woman presents to the emergency department with abdominal pain, vomiting, and confusion. She has a history of ovarian cancer diagnosed 1 year ago s/p chemoradiation treatment. On examination; temp: 39.20c, HR: 110 bpm, BP: 85/60 mmHg, and RR: 26 breaths/min. Physical examination reveals a diffusely tender abdomen but no rebound tenderness, rigidity, or palpable masses. Discuss her plan of management and differential diagnosis.

Management This patient presents with septic shock, a complication arising from a possible differential diagnosis of bowel obstruction (malignant/ non-malignant bowel obstruction) or pelvic infection. According to the Third International Consensus Definitions Task Force, sepsis is defined as "life threatening organ dysfunction due to a dysregulated host response to infection" [1].

Aggressive fluid resuscitation and empiric parenteral broad-spectrum antibiotics are required as initial management. Monitor vital signs and input/output as well as central venous pressure.

Sepsis is associated with organ failure. Comprehensive metabolic panel, liver function tests, and complete blood count are recommended laboratory studies. Leukocytosis can be seen in cases of pelvic infection, bowel obstruction, or sepsis.

Imaging may be done once the patient's condition is stable. Abdominopelvic CT with IV contrast is useful to rule out pelvic abscess, bowel perforation, or bowel ischemia. Pelvic abscess and bowel perforation are surgical emergencies, and early surgical management improves the outcome of the patient. It is crucial to evaluate the stage of the disease, patient's prognosis, and quality of life before considering surgical management as it is associated with high morbidity and mortality in terminal disease.

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The patient's nutritional needs should also be considered. Evaluate the need for parenteral nutrition and consider the benefits vs *the associated risks such as catheter infection, sepsis, and renal/hepatic failure.*

It is important to have an appropriate and adequate pain management plan for the patient. The goal of care especially in palliative cases must include patient comfort.

Introduction

Gynecologic cancer patients can suffer unexpected emergencies at any stage of disease and treatment. Emergencies may be due to complications of the disease, toxic effects of treatments used in managing the malignancies including chemotherapy, surgical procedures, and radiotherapy, as well as multifactorial underlying causes. Different approaches in handling each emergency depend on the etiology. In this chapter, we discuss emergencies and complications frequently encountered in gynecologic oncology. We will also review the management of these emergencies taking into consideration that goals of care should be dependent on the patient's disease status and prognosis.

Acute Blood Loss

Hemorrhage is a frequent and potentially life-threatening complication in gynecologic oncology. The causes of bleeding are related to tumor invasion, tumor angiogenesis, clotting factor deficiencies arising from hepatic impairment, and systemic effects of cancer, such as chemotherapy and radiation therapy [2].

Primary or recurrent neoplasms of the uterus, cervix, vagina, or vulva may present with small bleeds or with massive life-threatening hemorrhage. Hemorrhage due to metastasis can also be of varying degrees with massive hemorrhage signifying the terminal event in late-stage disease. The most common cause of bleeding in gynecologic malignancies is advanced cervical cancer. Due to the varied incidence and stage of diagnosis of cervical cancer in the world, studies report incidence of vaginal bleeding ranging from 0.7% to 100%, with an attributable mortality of up to 6% in these patients [3]. Palliative treatment options for bleeding are used in different health-care settings depending on available resources.

Many gynecologic surgical procedures are also associated with significant bleeding due to the vascular tumor surgical sites. While most of the causes and areas of bleeding can be controlled by conventional management, it is important to mention presacral bleeding, which is not easily controlled by standard management and often fatal. However, presacral bleeding is uncommon and is seen in gynecologic oncology procedures such as pelvic exenteration and radical hysterectomy [4].

Other significant causes of acute blood loss in gynecologic malignancies include hemorrhagic cystitis and radiation proctitis, both of which are late toxic effects of pelvic radiation.

Radiation proctitis is radiation-induced inflammation of the rectal mucosa occurring as a result of pelvic radiation therapy. The rectum is particularly susceptible to radiation injury due to its proximity to the pelvic organs and fixed position in the pelvis [5]. Acute radiation proctitis, which is usually self-limiting, occurs in the first 3 months of radiation treatment and may present with mild rectal bleeding and tenesmus. Chronic radiation proctitis occurs 3 months after completion of radiation therapy and presents with more overt bleeding due to predominance of fragile telangiectatic vessels and a friable mucosa.

Hemorrhagic cystitis (HC) is a common adverse effect of chemotherapeutic agents, such as cyclophosphamide and isofosphamide used in bone and soft tissue sarcomas and also as immunosuppressive agents for hematopoietic cell transplantation. In gynecologic cancers, HC has been described as a late toxicity of pelvic radiation treatment. Depending on the severity and the cause of hemorrhagic cystitis, different grading systems are used (Table 32.1).

Radiation-induced hemorrhagic cystitis may present in the acute or chronic phase. Acute radiation-induced HC occurs in 10% of gynecologic cancers treated with pelvic radiation [6] and presents with bladder pain that resolves ~ 4–6 weeks after the last fraction of radiotherapy. It is prudent to rule out a urinary tract infection, which presents with similar symptoms. The chronic phase of HC occurs 2–10 years post radiotherapy, and presents with bladder irritation and hematuria. This stage is irreversible. It is important to rule out bladder cancer, which can occur either as a primary disease or secondary late complication of pelvic radiation. Therefore, urinary examination, CT urogram, and cystoscopy with biopsy of lesions should be done to differentiate malignancy from chronic inflammation. Confirmation of chronic radiation inflammation is achieved by demonstrating that the inflammatory lesion occurred in the same site of radiation as per the dosimetry plan (Table 32.1) [7].

Severe hemorrhagic cystitis, though not common, has significantly high mortality despite vigorous treatment. A large study conducted to study the incidence, severity, timing, clin-

Table 32.1 Grading of hemorrhagic cystitis [8]

Grade	Features
0	No symptoms
1	Microscopic hematuria
2	Macroscopic hematuria
3	Macroscopic hematuria with small clots
4	Massive hematuria requiring clot evacuation

ical management, and outcome for patients who developed hemorrhagic cystitis following pelvic therapy for Federation of Gynecology and Obstetrics (FIGO) stage IB cancer of the cervix showed the incidence of HC to be 6.5%, with grade 3 occurring in 18% of the HC cases. After actuarial analysis, they demonstrated an increase in incidence with increasing duration from the last pelvic radiotherapy treatment [9]. Clinicians should be aware and recognize hemorrhagic cystitis emergencies that occur as late effects of radiation toxicity.

Management

Immediate assessment of hemodynamic stability is important for timely resuscitation to be initiated. Adequate volume replacement with crystalloids, followed by blood products, should be administered with frequent reassessment and monitoring of the patient's clinical status and vital signs. In patients with cardiorespiratory impairment, titration against central venous pressure may be necessary. Insert a Foley catheter to monitor output and also to avoid urinary retention by inserting prior to vaginal packing. Management depends on individual needs including platelets and clotting factors replacement. Depending on the cause, options to control bleeding include non-invasive and invasive methods.

When the cause of bleeding is due to advanced cervical cancer, palliative interventions have been used with no single intervention demonstrated to be more superior. Resources play a major role regarding the choice of intervention used in the management of bleeding [3]. Non-invasive techniques are utilized first to control hemorrhage, and when these fail, more invasive methods are applied.

Non-invasive Bleeding Management Vaginal packing is a simple initial measure to control vaginal bleeding, a common presentation in advanced cervical cancer. Sedation or short-acting general anesthesia may be utilized to ensure patient comfort. The source of bleeding is visualized and by use of speculum, the vaginal fornices are packed tightly to maintain an even pressure on the bleeding vessels. Measures to enhance the effectiveness of the packing include decreasing patient mobility, elevating the foot of the bed, and using hemostatic agents (oral, local, or parenteral). Tranexamic acid is an example of a parenteral agent that increases clotting by inhibiting plasmin in the clotting cascade. Topical/locally acting hemostatic agents can be used, including Monsel solution, formalin, and Moh's paste [3, 10].

Monsel solution(ferric subsulfate) can be applied directly on the bleeding site on the cervix or soaked in the vaginal pack and causes agglutination of protein resulting in sealing of the blood vessels [3]. Although Monsel solution has been reported in numerous studies as an excellent hemostatic agent, great care should be observed that minimal amounts of the solution are used. Due to its action, it can induce full-thickness necrosis, perforation, and life-threatening peritonitis when exposed to the peritoneal cavity [11]. Moh's paste has been used as a safe and effective method in cases of vaginal bleeding due to advanced cervical cancer though clinical trials are warranted for adoption of widespread use. It works by releasing zinc ions when in contact with cervical tumors and precipitates wound proteins to enhance hemostasis [12]. Formalin has been used in limited resource settings to enhance the effectiveness of the vaginal pack by acting as a chemical cauterization agent inducing contact coagulative tissue necrosis of the neovasculature to stop bleeders [10]. Formalin is also used to control bleeding in radiation proctitis with documented success rates of up to 75%. Caution must be taken to prevent damage to normal rectal mucosa, which can cause anal pain, strictures, fistulas, and stool incontinence [5, 13]. (Detailed management of radiation proctitis is covered in another chapter of the book.)

When using a vaginal pack to control bleeding, oral broad-spectrum antibiotics and metronidazole are required to treat underlying infections that are common in necrotic, bleeding tumors [10].

Another non-invasive method to control bleeding in gynecologic tumors is hemostatic radiotherapy.

Hemostatic radiotherapy (RT) is effective for emergent palliation of bleeding tumors with lower recurrence of re-bleed and minimal treatment burden for patients with advanced disease. Short-course hypo-fractionated RT is effective and well-tolerated for vaginal bleeding control in 93.8% of patients with advanced cervical cancer, with an additional benefit of pelvic pain control in 66.7% of the patients [14]. Comparable results have been reported of symptomatic relief of vaginal bleeding in 85–100% of patients when treated with two or three 10 Gy fractions of pelvic radiation therapy [15]. More evidence also supports palliative-dose radiotherapy at standard curative treatment fraction of 1.8–2.0 Gy in a single-dose fraction effective for vaginal bleeding in cervical cancer [3, 10].

Invasive Bleeding Management Invasive methods such as interventional radiology and surgery are reserved for use in cases of uncontrolled bleeding in carefully selected patients due to associated morbidity. Uterine artery embolization using metal coils, foam, or glue-like agents is done by the interventional radiology (IR) team, and when IR is not available, laparotomy with ligation of vessels (uterine artery and divisions of the hypogastric arteries) serve as an alternative [4].

Hemorrhagic Cystitis Treatment Radiation-induced hemorrhagic cystitis poses challenges in management due to the ischemic nature of the disease. There are no existing guide-

lines and clinical trials for treatment. Resuscitation with fluids or blood products should be used for hemodynamically unstable patients while carefully monitoring the vital signs and central venous pressure.

Management depends on the severity and grading of HC. Various options are used to alleviate symptoms, including steroids, vitamin E, trypsin, intravesical therapy with formalin and hyaluronic acid for clot evacuation and chemical cauterization, and hyperbaric oxygen with varying degrees of success. Visualization of the fragile telangiectatic vessels by cystoscopy and selective embolization of the bleeders can be used after non-invasive steps are ineffective. Surgery may be considered for refractory cases as a last treatment option. Strict dose constraints to the bladder and tailoring the field are employed to reduce the incidence of hematuria [7, 8, 16].

Summary: Management of Hemorrhagic Cystitis (Fig. 32.1) [7]

Pelvic Infections

Radical gynecologic oncology surgery is associated with a high rate of postoperative complications. Gynecologic procedures increase the risk of pelvic infections due to migration of potential microorganisms from the skin, vagina, and endocervix [17].

Additionally, inefficient defense mechanisms as seen in gynecologic cancer patients, impaired venous or lymphatic circulation after radical hysterectomy or radical vulvectomy [18], and a history of radiation therapy further increase the risks of infection [17].

Pelvic infections in gynecologic cancer patients included in this chapter are vaginal cuff cellulitis, pelvic cellulitis, and pelvic abscesses. Vaginal cuff cellulitis is an infection of the superficial tissues at the vaginal surgical margin, while pelvic cellulitis involves deep soft tissue at the incision.

Prior to routine antibiotic prophylaxis, pelvic infection rates post-hysterectomy were up to 33% [16]; however, widespread implementation of routine antibiotic prophylaxis has led to a significant decrease of pelvic infection rates to 2.7% [18, 19]. Other studies report that pelvic abscesses occur in 3.9% of patients within 30 days after surgery and 6.6% of patients as a late complication in post-trachelectomy for cervical cancer [20, 21].

Infections are often polymicrobial in nature, composed of both endogenous non-pathogenic and pathogenic bacteria. Frequently isolated pathogen includes Gram-negative bacteria, enterococci, group B streptococci, and anaerobes.

Typically, patients with pelvic abscess present with pelvic pain, fever, tachycardia, and tachypnea. On physical exam, the abdomen/pelvis is diffusely tender and a fluctuant mass may be palpable. Vaginal cuff cellulitis presents as acute onset of fever, chills, and macular erythema, with swelling over the lower abdominal wall and inguinal region, that may extend to the proximal thigh. The adnexa and parametrium are non-tender to physical exam. Pelvic cellulitis presents with fever, vague abdominal pain, and anorexia. Physical

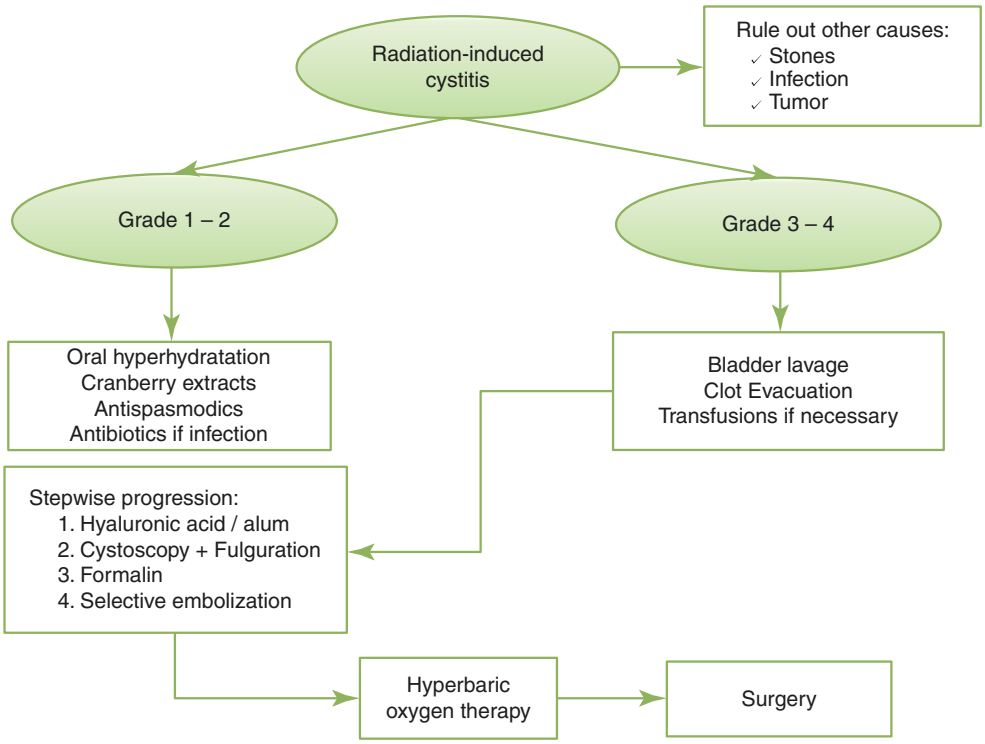

Fig. 32.1 Management of hemorrhagic cystitis. (From Liem et al. [7] with permission Springer Nature)

Table 32.2 Choice of antibiotic therapy for pelvic infections

Diagnosis	Treatment regimen	Notes
Vaginal cuff cellulitis	Amoxicillin/clavulanate 875/125 mg every 12 h *or* Ciprofloxacin 500 mg every 12 h with metronidazole 500 mg every 12 h *or* TMP-SMX DS every 12 h with metronidazole 500 mg every 12 h	Empiric broad-spectrum antibiotics outpatient management with close follow-up
Pelvic cellulitis	Clindamycin 900 mg every 8 h *or* metronidazole 500 mg every 12 h *plus* Penicillin five million units every 6 h *or* ampicillin 2 g every 6 h *plus* Gentamicin 5 mg/kg every 24 h In case of *renal impairment substitute gentamicin for aztreonam 2 g every 8 h*	Empirical inpatient parenteral broad-spectrum antibiotics, administered intravenously until patient is afebrile for 24–48 h and can then be discharged with oral antibiotic regimen for 14 days with close follow-up
Pelvic abscess	1. Metronidazole 500 mg every 12 h plus Ceftriaxone 2 g every 24 h[a] or 2. Piperacillin-tazobactam 3.375 g every 6 h or 3. Aztreonam *plus* clindamycin or carbapenem[b]	Empiric parenteral broad-spectrum antibiotics continued until patient is afebrile for 48–72 h and clinical improvement is seen. Choice of oral antibiotics should depend on culture and sensitivity results

[a]Recommended first line
[b]In case of penicillin or cephalosporin allergy

examination of pelvic cellulitis will reveal tenderness with absence of masses unlike pelvic abscess [18, 22].

Laboratory findings include leukocytosis, elevated erythrocyte sedimentation rate, and elevated C-reactive protein. Fluid collections in pelvic abscess can be visualized by ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI).

Management

Management depends on the clinical status of the patient and the characteristics of the infection. Initial assessment includes evaluation of the hemodynamic stability of the patient. Hemodynamically unstable patients are likely to have a ruptured abscess, which is life-threatening and requires prompt emergent surgical intervention. In addition, these patients require aggressive fluid resuscitation and empiric parenteral broad-spectrum antibiotics [22].

Vaginal cuff cellulitis is managed in the outpatient setting with broad-spectrum antibiotics and close follow-up to monitor treatment efficacy. Pelvic cellulitis and pelvic abscess require in-hospital management. Surgical abscesses require drainage if; the pelvic abscess is >8 cm, there is no adequate response/clinical deterioration to antibiotic treatment for 24–48 h, and progressively increasing abscess size [23]. There is sufficient evidence that suggests early drainage of all abscesses combined with broad-spectrum antibiotics is safe and improves clinical outcomes with reduced mean hospital stays [24, 25]. However, due to associated morbidity in these patients, the clinician should evaluate the increased risks versus potential benefits.

The suggested regimens (Table 32.2) are based on broad consensus rather than clinical trials. If the patient does not respond 48–72 h on treatment, consultation with an infectious disease specialist is warranted.

Gastrointestinal Emergencies in Gynecologic Cancer Patients

Malignant Bowel Obstruction

Acute intestinal obstruction is a surgical emergency that is often associated with pelvic tumors. It is a relatively common complication of advanced gynecologic malignancies with reported rates of 6% to 50% in patients with advanced or recurrent ovarian cancer and ~5% in cervical cancer [26, 27]. Bowel obstruction can be classified according to etiology as malignant bowel obstruction (MBO) or non-malignant bowel obstruction [26].

The causes of MBO in gynecologic cancer include peritoneal carcinomatosis, extrinsic bowel compression by tumor, adhesions, enlarged pelvic lymph nodes, tumor infiltration of the mesentery, bowel muscle or nerves, edema of the bowel wall, and post-radiation changes [28, 29].

In gynecologic cancer patients, MBO has a relatively poor prognosis with some studies reporting 3-month median survival rates. MBO has often been cited as a pre-terminal event for majority of the patients regardless of treatment. Therefore, the goal is palliative management for comfort and improving their quality of life [30].

Diagnosis of intestinal obstruction is made by presenting clinical symptoms and diagnostic imaging. Proximal bowel obstruction presents more abruptly with abdominal pain, nausea, and vomiting. Repeated vomiting may lead to metabolic alkalosis and hypokalemia. Distal bowel obstruction is more insidious and progressive in onset, presenting with prominent abdominal distension, abdominal pain, and constipation.

Plain abdominal radiography is the initial imaging of choice and demonstrates features of obstruction that include dilated loops of bowel with multiple air fluid levels [31]. Abdominopelvic computed tomography (CT) gives more clinical information, which is relevant in planning management. It determines presence and level of obstruction and complications of bowel obstruction such as ischemia or perforation of involved bowel, both of which are surgical emergencies [32].

Laboratory studies are also useful as they evaluate presence of complications such as metabolic derangements (acidosis, hyperkalemia) and leukocytosis which can be suggestive of infection.

Management The aim of management in gynecologic cancer patients with MBO is symptom control and maintain the patient's quality of life due to the associated high comorbidities and low median survival rates.

Therapy starts with conservative management, which includes restoration of fluid and electrolyte balance, alternatives for feeding, restriction of medication that have paralytic effect on the intestines, and nasogastric tube placement for decompression with stimulation of intestinal passage for distal obstructions [33]. This conservative regimen will keep the patient in optimal condition and allow time for to identify the origin of the obstruction, stage of the malignant disease, and obtain multidisciplinary evaluation. Conservative treatment provides time for diagnostic procedures as well as to see if the obstruction will resolve spontaneously, but no longer than 3–7 days [34, 35]. After this period of time, decisions have to be made either for surgery or refraining from intervention and providing symptomatic and supportive care.

There are contradicting clinical and ethical accounts supporting and against parenteral nutrition for patients with advanced malignancies receiving parenteral care. Patients with MBO have limited/no oral intake, and parenteral nutrition (PN) is a way of providing macro- and micronutrients, fluids, and electrolytes. There is still very low evidence whether parenteral nutrition plays a role in improving survival and quality of life in people with malignant bowel obstruction [36]. TPN has been shown to be of benefit only to improve immediate survival in patients who may otherwise die of starvation than the malignancy [37]. In retrospective studies, PN has been associated with improved survival in patients with a Karnofsky Performance Score (KPS) of greater than 50 [38]. However, the benefits of home PN in patients with inoperable malignant MBO are uncertain and must be balanced against risk of central line infections, thrombosis, electrolyte abnormalities, and increased cost with no associated increase in mean survival for the patient. Consider PN when the risk of starvation or malnutrition is higher than that of disease progression. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends PN should be offered if the expected survival with tumor progression is longer than 2–3 months [38].

When the cause of obstruction is benign, laparotomy should be performed for adhesiolysis or bowel resection [39]. In the case of radiation enteritis, it is important to resect the entire diseased bowel segment to reduce recurrence, postoperative complications, and mortality [40]. In malignant obstruction, surgical interventions such as bowel resection, bypass, or ileostomy may seem to provide good palliation by reduction of symptoms and obstruction recurrence in progressive disease, but these interventions depend on the extent of the disease in the individual patient [41]. Palliative surgery offers limited benefits in improving quality of life and survival. Family members should be involved in critical discussions prior to undertaking such drastic measures [36]. Surgery in patients with peritoneal carcinomatosis is related with a 30-day mortality of 21–40% and high recurrence rates [42].

Gastrointestinal Perforation and Fistula

Gastrointestinal (GI) perforation and fistulas are potentially life-threatening events that can develop in gynecologic cancer patients. Patients are prone to bowel injury of various forms, including complications arising from tumor invasion, pelvic radiation, and chemotherapy. Tumor invasion of the bowel is common in advanced ovarian, fallopian tube, and primary peritoneal cancers. Pelvic radiation, frequently used in advanced cervical cancer treatments, is a known cause of radiation-related bowel toxicities.

Bevacizumab, an antiangiogenic drug that was approved in 2014 for patients with advanced cancer, has significantly improved overall survival when used in combination with other chemotherapy agents. However, it is associated with clinically significant rates of GI fistula: grade 2 and grade 3 (requiring intervention), at rates of 5% and 3%, respectively. The risk of developing fistulas is increased by additional clinical factors such as concurrent tobacco use, pre-existing hypertension, pelvic tumor (as an independent risk factor), and pelvic radiation [43]. Gastrointestinal perforation in bevacizumab is a serious but uncommon adverse effect that has been well documented in phase III clinical trials, as well as subsequent surveillance trials, with reported incidence rates of 0–11% [44].

Paclitaxel has also been associated with GI perforations, and it is believed it is caused by cellular necrosis induced

by mitotic arrest of GI epithelium. The exact incidence is unknown. However, while it is infrequent, it has a high mortality rate of 57%. Therefore quick diagnosis and a high index of suspicion in a patient presenting with abdominal pain and neutropenic fever following paclitaxel chemotherapy are warranted [45, 46, 68].

Presentation of bowel perforation and fistulas may be asymptomatic. Non-specific signs also include diffuse abdominal pain and tenderness, fever, and tachycardia.

Sepsis is a life-threatening complication of GI perforation and presents with hemodynamic instability, altered mental status, hypothermia/hyperthermia, and organ dysfunction, including acute respiratory distress syndrome, acute renal injury, and disseminated intravascular coagulopathy. Elevation of inflammatory markers (C-reactive protein, serum amylase) may be present, but is non-specific.

Patients with a suspected bowel perforation should be evaluated by abdominopelvic CT, which has higher sensitivity than plain films and can demonstrate small amounts of extraluminal gas.

Management Initial management should include an assessment of hemodynamic stability and monitoring of electrolytes. Resuscitation with intravenous fluid therapy is the next step in management for hemodynamically unstable patients.

Bowel injury in patients with advanced gynecologic malignancies tends to have a poor prognosis independent of the bowel injury.

Depending on the clinical status of the patient, appropriate conservative or definitive surgical management should be instituted. Non-invasive interventions include broad-spectrum antibiotics and, depending on the level of perforation, appropriate drainage tubes. Patients with suspected perforation whose clinical condition is unstable require immediate surgical repair or diversion. Factors that should be considered before surgical management are the patient's comorbidities, general clinical health condition, and overall prognosis. Extent/stage of the malignancy at the time of bowel perforation is the main prognostic indicator regardless of the type of management approach. Patients with advanced disease may be appropriate candidates for less invasive management [47].

Genitourinary Emergencies in Gynecologic Cancer Patients

Vaginal Cuff Dehiscence

Vaginal cuff dehiscence is a rare, but devastating, complication of hysterectomies (common procedures done in gynecologic oncology) and is associated with high morbidity requiring urgent management. A large study review of hysterectomies reported an annual cumulative incidence rate of vaginal dehiscence of ~ 0.14% of total abdominal and vaginal hysterectomies. Various studies report a similar low incidence. There is a slightly higher incidence reported in laparoscopic- and robotic-assisted total hysterectomies [48, 49].

Patients with vaginal cuff dehiscence may present with abdominal pain, serous vaginal discharge, vaginal bleeding, and vaginal bulge, as well as with more severe complications, such as peritonitis and bowel evisceration.

Vaginal cuff dehiscence is a clinical diagnosis. A comprehensive physical and vaginal examination is adequate to make a definitive diagnosis. Recommended laboratory studies include a metabolic panel and complete blood count. Leukocytosis can signify complications such as infection, peritonitis, and bowel ischemia/injury. Imaging such as abdominopelvic CT may be used to rule out complications and comorbidities such as pelvic abscess, bowel injury, and hematoma [50].

Management The clinical status of the patient is an important aspect to consider in management of vaginal cuff dehiscence.

Initial management includes resuscitation of the patient with fluids and/or blood depending on the hemodynamic status of the patient. Broad-spectrum antibiotics that adequately cover for Gram-negative and anaerobic organisms (ampicillin, gentamicin, and clindamycin) should also be administered [50].

Expectant or definitive management is dependent on the patient's clinical status, size of the defect, and presence of bowel evisceration. Peritonitis and bowel evisceration are surgical emergencies. If bowel evisceration is present, while waiting to take the patient to the operating room, insert a Foley catheter, position the patient in Trendelenburg, and cover the bowel with a warm moist towel, frequently irrigating the structures with warm normal saline. The surgical approach relies on the surgeon's experience and status of bowel viability. Intraoperatively, in the absence of infections and with signs of viable bowel, the prolapsed bowel can be gently reduced to the peritoneal cavity transvaginally. Other surgical approaches include abdominal, laparoscopy, or a combination of both. Debridement of necrosed tissue, dissection, and bowel resection are common intraoperative procedures for surgical management of vaginal cuff dehiscence [51, 52].

Urinary Tract Obstruction

Urinary tract obstruction is an important cause of renal failure in gynecologic cancer patients, especially in advanced cervical cancer. Obstruction can be caused either by extraluminal compression on ureters or direct infiltration of tumor into ureters. Benign causes for acute obstruction of urinary

tract in cancer patients can be fibrosis or pelvic inflammatory disease after surgery, catheter-induced edema, or strictures after radiation therapy [53].

Tumors causing obstruction include cervical cancer (most common), ovarian cancer, and other pelvic tumors. Large pelvic masses such as ovarian cancer can cause bilateral ureteric obstruction [54]. When bilateral obstruction develops, it leads to anuria and renal failure, with progressive rise in serum creatinine [55].

Commonly, obstruction of the urinary tract leads to hydronephrosis. Ultrasound of the abdomen, cystoscopy, retrograde ureteric investigations, and CT scan are helpful diagnostic options in assessment of the etiology and extent of the obstruction.

Management The basic principle of management is decompression of ureters because it preserves renal function [56]. This can be accomplished by percutaneous nephrostomy or cystoscopy and retrograde placement of an internal ureteric stent [56, 57, 69]. Percutaneous nephrostomy is a temporary measure used for patients with undiagnosed malignancy or in patients with cervical cancer who have available treatment modalities and a good chance of treatment response. Ureteric stent insertion is reserved for patients with advanced malignancy for palliative relief of the obstruction and associated symptoms.

Pain

Acute pain is the most common symptom in gynecologic malignancies and is the leading cause of emergency department visits [58, 59]. Several retrospective studies have shown that gynecologic cancer patients have higher rates of moderate to severe pain and higher rates of opioid use as compared to patients with other solid tumors [60].

In advanced cancers, pain can be caused by involvement of the regional nerves, pelvic muscles, and bones. Pelvic tumors can also encroach the presacral area causing visceral pain. The mechanisms of pain are not completely understood and are thought to include tissue destruction or stimulation of cytokine secretion [61].

Pain management depends on the mechanism and location of pain. The American Pain Society recommends the prompt treatment of patients with acute pain with numerous trials advocating multimodal therapy [61]. For patients with acute uncontrolled pain not responding to oral or IV analgesics, techniques such as epidural opioids and neurolysis can be used [10]. The National Comprehensive Cancer Network (NCCN) also confirms the use of opioids for severe to moderate pain and non-opioids as adjuncts. Neuropathic pain is frequently resistant to opioids and adjuncts such as tricyclic antidepressants (TCAs), selective serotonin receptor inhibitors (SSRIs), and gabapentin can be considered although there are limited clinical trials attesting to their efficacy [62].

The revised World Health Organization (WHO) analgesic ladder (Fig. 32.2) describes a simple four-step bidirectional approach for pain management, with opioids being the cornerstone of treatment for active cancer pain [63]. This approach should be used with caution due to the risk of opioid dependency and misuse. The American Society of Clinical Oncology (ASCO) policy statement on the use of opioids in the cancer population states that access to opioids must be assured, and law and regulations intended to address abuse and overdose should be crafted to avoid creating impediments to this treatment [64]. The European

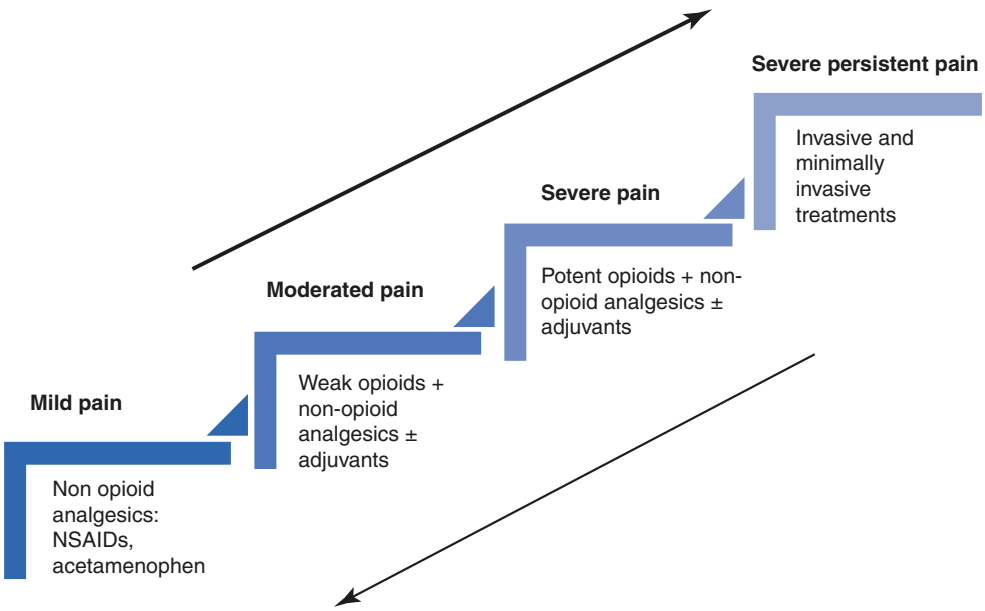

Fig. 32.2 The revised WHO analgesic ladder [63]

Association for Palliative Care advises that the skilled use of opioids is crucial to the relief of cancer pain [65].

Palliative radiation therapy is the standard for management of pain in bone metastasis. Radiation therapy (RT) has been proven to provide effective palliation of painful bone metastases with few adverse effects. The American Society for Radiation Oncology (ASTRO) has strong recommendations based on high quality evidence for the use of palliative RT for pain management. Updated reviews show equivalent pain relief for single fractions for patients with previously unirradiated bone metastases, with no increased risk for pathologic fractions, as with fractionated therapy. This is desirable and convenient for patients with advanced disease and limited life expectancy [66].

Conclusion

Emergencies in patients with a history of gynecologic malignancy can occur at any time during the course of cancer disease. Specific features of emergency presentations in these patients require knowledge of the patient's cancer history and medical knowledge of principles that should be applied in emergency situations. Therapy is individually tailored and depends on the underlying cause for the emergency, stage of the malignant disease if still present, previous cancer treatments, and immunological and general condition of the patient. Prompt therapy is crucial and diagnostic imaging should not delay initial management. Computerized tomography imaging guidelines and early gynecologic oncology consultations have significantly decreased CT utilization rates in the ED, therefore avoiding unnecessary imaging [67].

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Orthopedics

33

Robert C. Weinschenk and Patrick P. Lin

Case Study

A 57-year-old female with no known primary cancer presents to the emergency department (ED) with a 3-week history of progressive right groin pain. She denies any associated trauma. She previously ambulated independently without assistive devices, but now requires a cane. Her pain is most significant when ambulating, but she admits to pain at night and at rest. Over-the-counter pain medication has been ineffective. She denies any numbness, tingling, or weakness.

On physical exam, she has no gross neurovascular deficits, but is unable to perform straight leg raise and has marked pain with passive internal rotation of the right hip. Radiographs show a large lytic lesion in the femoral neck, which combined with her pain, results in a Mirels' score of 12 (Fig. 33.1). Laboratory workup is remarkable for an elevated TSH. CT of the chest, abdomen, and pelvis shows an enlarged thyroid, and bone scan shows no additional sites of bony disease.

The patient underwent core needle biopsy of her femoral neck lesion and was diagnosed with metastatic follicular thyroid carcinoma. She underwent total hip arthroplasty followed by postoperative radiation. She additionally underwent a complete thyroidectomy.

Introduction

Orthopedic emergencies are common in oncologic patients because of the prevalence of cancer and secondary effects of oncologic treatment. While the anatomic considerations are the same as those in the general population, the altered biology and physiology consequent to cancer can increase the complexity of treatment. Providers must consider tumor histology, natural history of underlying disease, disease stage, and overall prognosis to achieve optimal, individualized care [1]. With that said, some of the more prevalent emergencies seen in the musculoskeletal oncologic have common features, such that an organized and systematic approach will set the physician up for success.

Trauma

Although the term "trauma" is usually associated with high-impact injuries, it also includes harm that occurs with minor force, which may pertain more to oncologic patients. In general, the core principles of trauma apply to oncologic patients, but there are several important distinctions for this population.

Pathologic Fractures

Pathologic fractures comprise a large portion of orthopedic oncologic emergencies, as they occur in 9–25% of patients with bone metastases [1]. The most common site is the proximal femur. In addition to pain and tenderness, patients may present with ecchymosis, deformity, edema, and joint effusion. The occurrence of a pathologic fracture can be the result of a long, complex process. Once disease is present in bone, it manipulates local biology, induces osteoclastic bone resorption, and ultimately causes loss of structural integrity.

Recognizing fractures as pathologic may not always be straightforward. This is particularly true for patients who present to the emergency department (ED) without a cancer diagnosis. Many patients are elderly with presumed osteoporosis. X-rays may be misleading because comminution around a fracture can hide a pre-existing bone lesion (Fig. 33.2). Failure to diagnose a fracture as pathologic can lead to grave consequences, including inappropriate surgery, delays in cancer treatment, and even loss of the limb.

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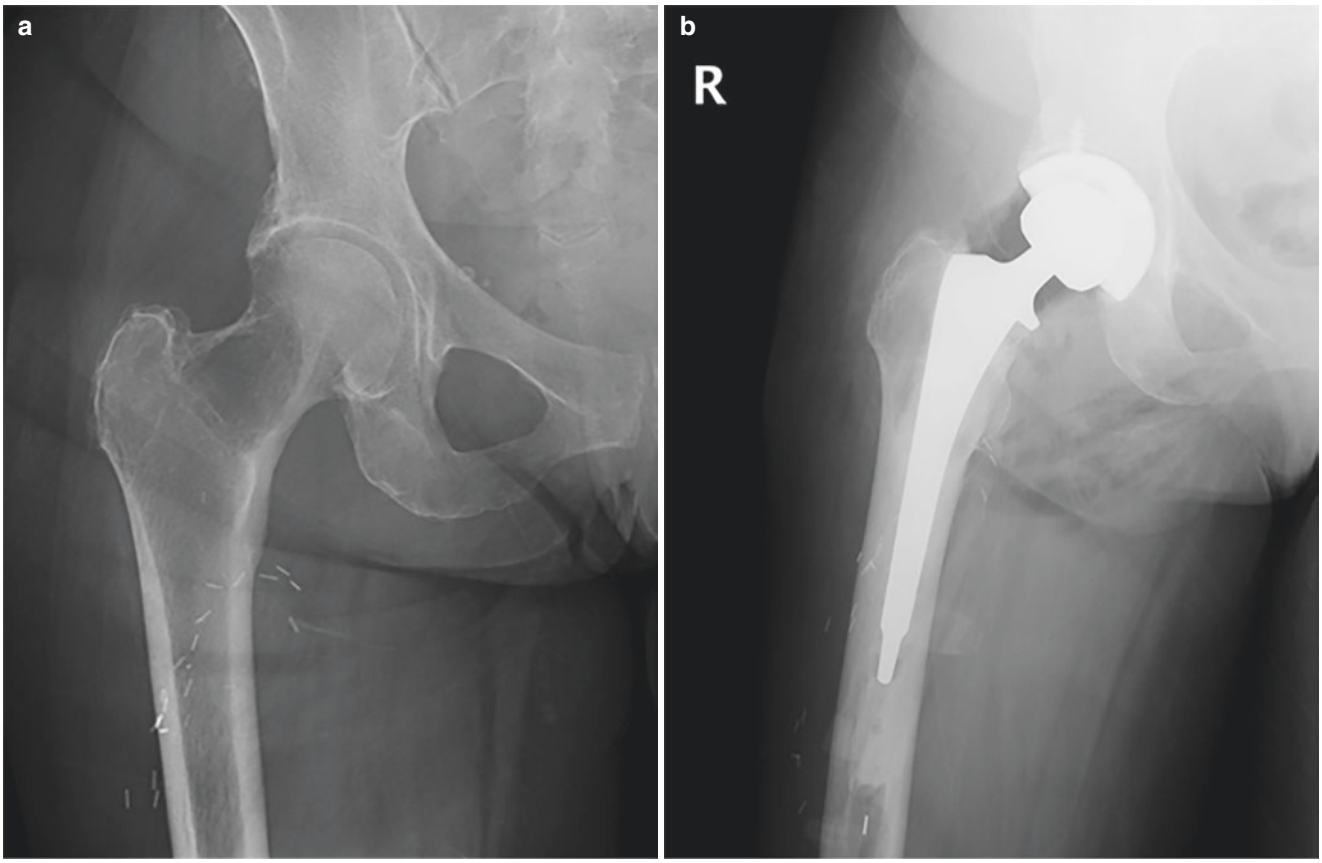

Fig. 33.1 (**a, b**) Preoperative and postoperative radiographs, respectively, of a 57-year-old female with metastatic thyroid carcinoma to the right femoral neck. Based on peritrochanteric location, lytic nature, large size, and significant pain clinically, Mirels' score of this patient is 12, and thus, prophylactic surgery was recommended

The history is critical. Certain diseases, such as breast and renal cancer, can present years after the initial diagnosis with metastatic bone disease as the first manifestation of relapse. The practitioner should inquire about pre-existing pain. A deep-seated, constant ache prior to fracture should raise suspicion of an insidious process in the bone. Systemic signs such as weight loss, night sweats, and fatigue are relevant clues. The mechanism of injury can be revealing as minimal trauma, such as rolling over in bed, can result in pathologic fractures. In general, a break that occurs with a force equivalent to (or less than) a fall from a standing height suggests a pathologic fracture.

Most pathologic fractures are best treated surgically. The pain relief from surgical stabilization is far superior to the analgesia of opioids. If a patient has extensive metastatic disease, palliative surgery is still justified if the patient is expected to live for >1 month. Not offering an orthopedic consultation simply because a patient has advanced disease can be a mistake.

On the other extreme, it is also errant to perform surgery prematurely. Because metastases are common and pathologic fractures cause severe pain, it is easy to fall into the trap of rushing to surgery. Without clear cancer staging indicating metastatic disease, it can be grossly negligent to operate on a presumption of metastasis. Primary sarcomas can also be a cause of pathologic fractures. A common mistake is nailing a lesion, which later turns out to be primary osteosarcoma. This frequently results in amputation due to marrow and soft tissue contamination.

When the etiology of a pathologic fracture is uncertain, additional preoperative workup is necessary. Imaging includes whole body bone scan, chest radiographs, and CT scan of the chest, abdomen, and pelvis [2]. Not only will this help identify other sites of disease, but it will also help identify the most accessible lesion to biopsy [1]. The most common primary carcinomas to metastasize to bone are breast, prostate, thyroid, lung, and kidney [3]. To help make a specific diagnosis, laboratory workup may include serum and urine protein electrophoresis (SPEP/UPEP) to assess for myeloma, thyroid-stimulating hormone (TSH), and prostate-specific antigen (PSA). A complete blood count (CBC) and inflammatory markers (erythrocyte sedimentation rate (ESR) and C reactive protein (CRP)) may be helpful if osteomyelitis is in the differential diagnosis.

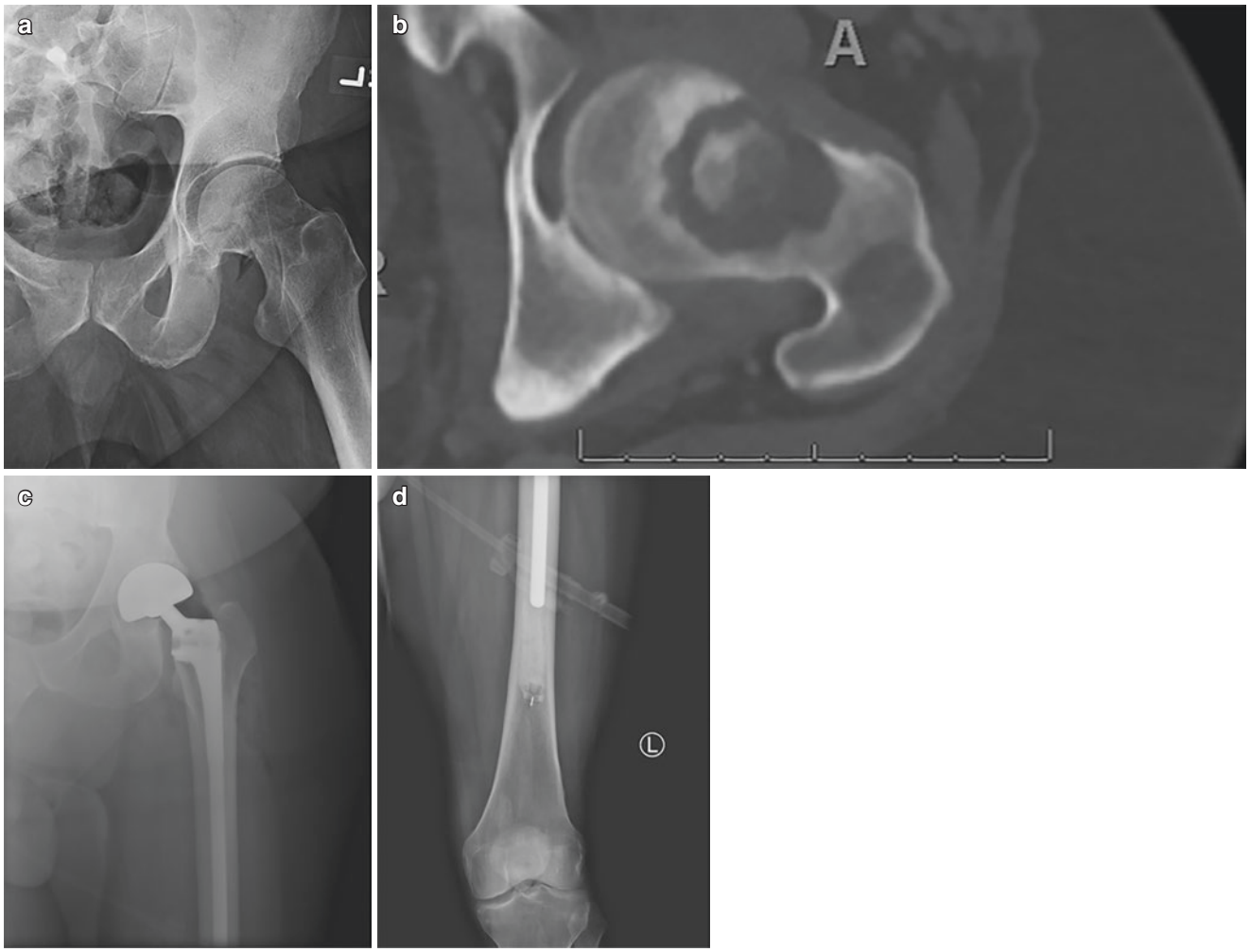

Fig. 33.2 A 43-year-old male with metastatic renal cell carcinoma, recent ground level fall with new inability to bear weight, with some preceding left hip pain. Initial X-rays show a displaced left femoral neck fracture, which could easily be mistaken for an osteoporotic fracture (**a**). CT scan illustrates a discrete metastatic lesion in the femoral neck that predisposed to this fracture (**b**). Patient underwent a left hip hemiarthroplasty (**c, d**)

Oncologic patients undergoing preoperative workup require additional special considerations. Orthogonal radiographs should be obtained of the entire bone, including the joints above and below the lesion. This clarifies the region of interest, identifies concomitant areas of concern, and aids in preoperative planning. Some patients have anemia, thrombocytopenia, or neutropenia. Extensive osseous metastasis can also cause marked hypercalcemia requiring pharmacologic correction [4]. Coagulopathy may be present because of cachexia, poor nutrition, or liver disease. Bedridden patients may be prone to venous thromboembolism. Cross-matched units of packed red blood cells need to be available, since metastatic lesions can bleed profusely intraoperatively. A chest X-ray prior to surgery can help screen for malignant pleural effusions.

When immediate surgery is not possible or prudent, appropriate immobilization is necessary. In general, long bone fractures should be immobilized in a well-padded splint that is not circumferential, to accommodate swelling. A joint above and joint below should be immobilized for mid-shaft fractures to prevent rotational stress. Exceptions to this include proximal humeral fractures and femoral fractures. Proximal humeral fractures can be immobilized in a cuff and collar or shoulder immobilizer. While some advocate Buck's traction for proximal femur fractures, current data do not indicate a clear benefit [5].

Surgical treatment of pathologic fractures has gradually become less invasive and stressful. In many instances, the fractures are amenable to intramedullary nailing, which can be placed percutaneously with minimal dissection. Nailing of proximal femoral metastases not involving the femoral head has been shown to be a reliable option with a 10% revision rate due to disease progression, breakage, and other reasons [6]. For pathologic fractures involving the femoral

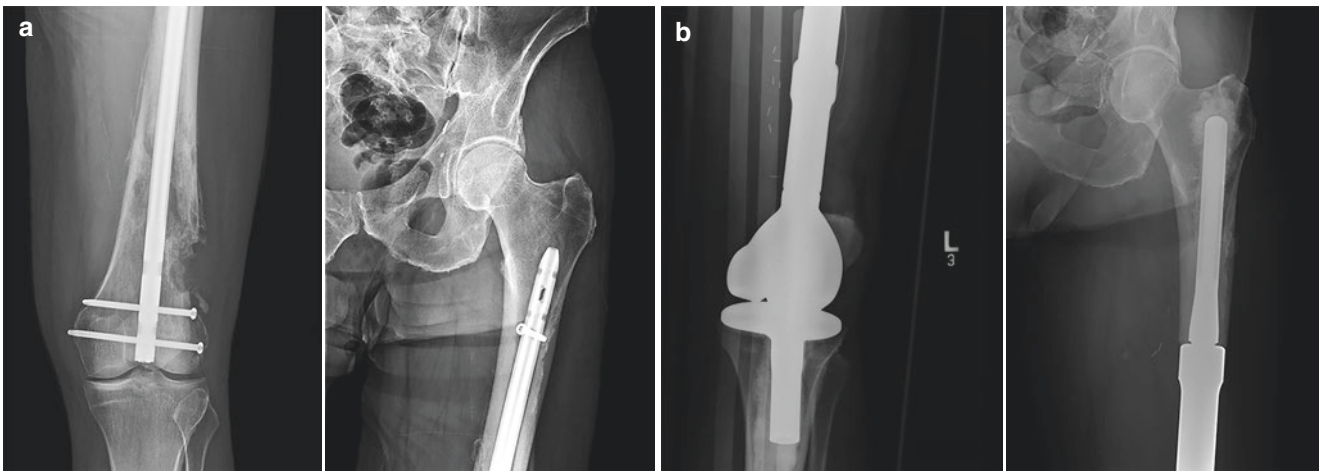

Fig. 33.3 A 61-year-old male with metastatic renal cell carcinoma to the left femur, 3 months status post intramedullary nailing at an outside facility, with progressive disease, difficulty ambulating, and persistent pain (**a**). The nail was removed and converted to a distal femur megaprosthesis (**b**), resulting in significant pain relief and improvement in function, as he was able to weight-bear immediately

neck and head, hip arthroplasty may be more secure than nails (see Figs. 33.1 and 33.2). These operations can also be done now through relatively small (10–15 cm) incisions. In the uncommon scenario where extensive bone destruction is present, larger segmental endoprostheses may be required, as nails may be structurally inadequate and fail to relieve symptoms (see Fig. 33.3).

Impending Pathologic Fractures

Impending fractures represent a form of orthopedic emergency, and, when diagnosed properly, are a best-case scenario. Prophylactic surgery prior to fracture results in less stress to the patient and a shorter hospital stay [7]. Additional benefits include improved pain control, diminished opioid use, better quality of life, simpler surgery, decreased operating time, and less blood loss [1]. For these reasons, emergency providers must be able to recognize the signs and symptoms of impending fractures.

Pain is the most common sign indicating an impending pathologic fracture. The degree of pain often correlates with degree of structural compromise of the bone. Patients may at first attribute pain to a presumed injury, but notice later that pain does not improve with time. Pain can be exacerbated by weight-bearing but is classically present at rest and at night [8]. In pelvic and femoral lesions, back and lower extremity pain is often coupled with mechanical instability [4].

The most common way to gauge the risk of impending fracture is Mirels' score, which incorporates four categories: pain, location, size, and radiographic appearance (see Fig. 33.1). Each category is given 1–3 points, depending upon the severity: pain (mild, moderate, functional), location (upper extremity, lower extremity, peritrochanteric in the proximal femur), size relative to bone diameter (<1/3, 1/3–2/3, >2/3), and radiographic appearance (osteoblastic, mixed, lytic). The total score ranges from 4 to 12. With a Mirels' score of ≥9, the risk of pathologic fracture is >33% and prophylactic surgery is recommended. A Mirels' score of ≤7 typically is treated nonsurgically with radiation. A Mirels' score of 8 is left up to surgeon discretion [9].

Mirels' score is widely employed, in part because it uses simple radiographs. However, reliance upon two-dimensional representation also limits its accuracy. In certain instances, CT scans can be helpful, since they provide three-dimensional detail regarding bone integrity and calcium density. While researchers have developed experimental methods of determining bone strength from CT scans that are more sensitive and specific in predicting pathologic fracture risk, these instruments are not yet available for widespread use [10].

In 22–30% of cases, patients with impending fractures do not have a known primary tumor at the time of presentation [2]. For adults over 40 years old, the differential diagnosis of a lytic lesion in bone includes metastatic disease, multiple myeloma, lymphoma, primary bone malignancy (sarcomas), destructive benign bone tumors (such as giant cell tumor of bone), and nonneoplastic conditions [8]. That being said, in this older age group, the most common malignant tumor of bone is metastatic disease, with the skeleton representing the third most frequent site of metastasis for carcinoma [2].

Open Fractures

While open injuries in cancer patients are mostly due to low-energy mechanisms, they should not be dismissed lightly, and it is important to follow Advanced Trauma Life Support (ATLS) protocols. Of those with open fracture, 30% have more than one injury [11]. One should check airway, breathing, and circulation, followed by a thorough head to toe exam after removing constricting clothing. The deadly triad of acidosis, hypothermia, and coagulopathy is common in these patients, and it is imperative to correct these abnormalities quickly. Open injuries should be scrutinized for signs of contamination and exposed bone. If a limb is grossly deformed, it should be gently reduced prior to splinting. In the absence of an open injury, but with significant skin tenting, causing vascular compromise to the skin, a reduction maneuver is also worth performing [11]. Patients should be examined for signs of vascular injury, which may include decreased/absent pulses, severe hemorrhage, expanding and pulsatile hematoma, bruit or thrill, numbness or neurologic deficit, decreased skin temperature, absent venous filling, absent pulse oximeter reading, or no capillary blanching [11]. If there is concern for vascular injury, a CT angiogram should be performed and a vascular surgery consultation obtained. All open wounds should be copiously irrigated prior to splinting, unless the patient is immediately being taken to the operating room. Due to environmental contamination, it is not recommended to obtain routine cultures from open wounds [11].

Early antibiotics are critical. Studies show that the most important factor in reducing infection rate for open fractures is early administration of intravenous antibiotics, ideally within 3 h of injury [12]. Open fractures are categorized by the Gustilo-Anderson classification: Type I (no gross contamination, laceration <1 cm, no significant muscle damage), Type II (+/− gross contamination, laceration 1-10 cm, no significant soft tissue crushing), and Type III (high energy, may have gross contamination, laceration >10 cm, extensive soft tissue injury). Type III is subdivided into types A (adequate soft tissue coverage), B (inadequate soft tissue coverage of bone), and C (vascular injury that requires repair). In general, Type I and II injuries are treated with a first-generation cephalosporin; for Type III injuries, add an aminoglycoside, and for farm injuries, add penicillin G. [13, 14]. All patients with open fractures must be asked about tetanus immunization history. Those who have had a booster in the past 5 years require no treatment. Those who have not had a booster in more than 5 years require tetanus toxoid plus human tetanus immunoglobulin (HTIG) if the wound is tetanus prone. Those who have not had a booster in more than 10 years or are immunocompromised require tetanus toxoid and HTIG [15].

Compartment Syndrome

Compartment syndrome is a problem that emergency providers must know how to identify, as it often demands immediate surgery. However, in the oncologic patient, compartment syndrome is usually not due to high-energy trauma but rather hematologic problems, and patients may not be good surgical candidates. The management thus has some unique features.

Compartment syndrome is a clinical diagnosis based on history and physical exam [16]. Fracture of the tibial diaphysis is the most common etiology, accounting for 36% of cases of acute compartment syndrome, with all four compartments frequently involved, but anterior compartment being most common [17]. Additional causes include blunt soft tissue injuries, burns, casts, venous thromboembolism, electromyelogram, extravasation of contrast, hematologic diseases, infection, hematomas, osteotomies, prolonged immobilization, and vascular procedures [18]. Pertinent laboratory values include creatine kinase, creatinine, BUN, potassium, urinalysis, and renal myoglobin. Rhabdomyolysis, which is frequent, causes renal insufficiency and hyperkalemia [18].

Classic findings include the 5Ps: pain, pulselessness, paralysis, paresthesia, and pallor. It should be stressed that excessive reliance upon the signs could lead to misdiagnosis since they may not be evident until late. Pain is usually the first symptom seen, typically due to ischemia and is often out of proportion to what is expected [19]. More specifically, pain occurs with passive stretch of the affected compartment (e.g., anterior compartment of tibia when ankle is passively plantar flexed). Marked firmness of the muscles, which is not one of the "Ps," is a reliable finding that is consistently present, but appreciation of muscle firmness requires some experience and can be difficult in obese or edematous limbs. Paralysis and pulselessness are usually very late findings after prolonged ischemia. Ironically, pulses may occasionally be bounding since the blood flow bypasses the capillaries in muscle, and this may lead the unwary clinician astray.

Although the diagnosis is usually evident from clinical examination, the findings are sometimes equivocal, especially for obtunded or mentally impaired patients. In these situations, an invasive diagnostic procedure can be performed to measure compartment pressures. A special manometer (i.e., Stryker Needle) is most commonly used. In the lower leg, all four compartments should be measured, ideally within 5 cm of the fracture site to improve diagnostic accuracy [20].

It is critical not to delay diagnosis or treatment. Duration of muscle ischemia predicts degree of muscle necrosis, and the damage to muscles becomes irreversible after 6 h of complete ischemia. On rare occasions, inflammatory response

that ensues can become systemic and ultimately lead to multiple organ failure [19]. Once diagnosis is established, the patient is taken to the operating room emergently for fasciotomy. The fasciotomy wounds are typically left open until the edema and swelling subside.

While compartment syndrome usually occurs after trauma in the general population, cancer patients more likely have a different etiology. Many have thrombocytopenia or coagulopathy secondary to either the disease or its treatment. When the platelet count is less than 10,000 per microliter, patients are at risk for spontaneous bleeding [21], which could cause acute compartment swelling.

Oncologic patients may not be appropriate for fasciotomies. Neutropenia, defined as absolute neutrophil count (ANC) of $<1.5 \times 10^9$/L, is one relative contra-indication to surgery and predisposes patients to wound infections [22, 23]. However, some clinical judgment must be exercised, and fasciotomies may be performed with mild degrees of neutropenia. A more problematic issue is a delayed diagnosis of compartment syndrome. For patients without clear trauma and fracture, this may not be recognized until days after onset, particularly when patients are heavily sedated in the ICU. If compartment syndrome is diagnosed late, after myonecrosis has already occurred, it may be a grave mistake to perform fasciotomies and to leave wounds open, as the dead tissue becomes prone to severe, deep infections. In this situation, surgeons may opt to delay intervention and address muscle contractures at a later date.

Infection

Orthopedic infections represent a major category of oncologic emergencies because many patients are immunocompromised. Not only does this make patients more susceptible to contracting infections, but also, the severity of infections can be much greater. Infections can involve soft tissue, bones, joints, or all three. In some cases, infection is insidious and indolent, but in others, it can be sudden and rapid. A prevailing theme in infection is that acute phase reactants can be a clue not only to presence of infection, but also to timing. In general, ESR has a high specificity for infection and malignancy, rises within 24–48 h of onset, and gradually resolves. CRP begins rising 12–24 h after onset and peaks in 2–3 days. Procalcitonin begins rising within 3–4 h and peaks within 6–24 h [24].

Cellulitis

Cellulitis is a diffuse, permeative infection of soft tissues that does not produce a loculated fluid collection or drainage. It presents as erythema, warmth, pain, swelling, and sometimes fever. Cellulitis is common in the oncologic population for several reasons, including immunosuppression and frequency of minor procedures, such as venipuncture. The differential diagnosis includes septic arthritis, necrotizing fasciitis, lymphangitis, insect bite, foreign body reaction, abscess, osteomyelitis, inflammatory conditions, muscle hemorrhage/hematoma, Sweets syndrome, and venous thromboembolism [25–27]. Noninfectious inflammatory conditions can be especially difficult to distinguish from cellulitis. These include gout, pseudogout, tenosynovitis, degenerative joint diseases, and rheumatologic conditions [25], all of which may be exacerbated acutely by chemotherapy.

Cellulitis is often a diagnosis of exclusion. Examination is useful for determining the likelihood of joint involvement and the presence of fluctuance. X-rays may help to rule out osteomyelitis [27], while ultrasound, MRI, and/or CT may be necessary to rule out loculated fluid collections and involvement of bone or joint. MRI characteristically shows diffuse edematous changes, bright on T2-weighted images, in cellulitis. Patients should be treated with empiric antibiotics since blood cultures are positive in <5% of patients [27]. The offending organism is most often streptococci or *Staphylococcus aureus,* and initial antibiotics should target Gram-positive bacteria [27]. Drawing a line around the region of erythema with indelible ink is helpful to track response to therapy. Depending on the degree of neutropenia, hospital admission for broad-spectrum intravenous antibiotics may be indicated.

Necrotizing Fasciitis

Necrotizing fasciitis is an acute, life-threatening infection that even among healthy individuals has a high mortality rate. It is imperative that this disease process be recognized early to maximize chances of survival. It is characterized by rapidly spreading inflammation followed by necrosis of fascial planes and surrounding soft tissue [28]. As many as 60% of patients have underlying diabetes [28]. Other risk factors include alcoholism, end stage renal disease, cardiopulmonary disease, peripheral vascular disease, advanced age, cancer/chemotherapy, immunosuppression, malnutrition, trauma, surgery, IV drug abuse, and smoking [28, 29]. Comorbid conditions that correlate with mortality include cancer, renal disease, and congestive heart failure [30]. Metastatic carcinoma has also been reported to cause a soft tissue abscess that ultimately led to development of necrotizing fasciitis [31].

Recognizing early signs and symptoms of necrotizing fasciitis is crucial but can be difficult, as pain frequently precedes overt findings [28]. Systemic symptoms include fever, chills, hypotension, and tachycardia. While patients may not have frank altered mental status, family mem-

bers often report that the patient is not behaving normally. Common skin findings, in addition to erythema and induration, are blisters and bullae that at first drain serosanguinous fluid and later become hemorrhagic. If there is associated soft tissue gas, crepitus will be present. A characteristic frequent finding of this disease is "dishwater pus," which describes the thin, watery, foul-smelling fluid produced consequent to necrosis of superficial fascia and fat [32]. The most common site of infection is the lower extremity, followed by the upper extremity and trunk [33].

Laboratory tests include CBC, comprehensive metabolic panel (CMP), ESR, and CRP. A useful diagnostic tool is the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) Score, which has a reported PPV of 92% and NPV of 96% [34]. The LRINEC score considers CRP (≥150 mg/L – 4 points); white blood cell (WBC) count (<15/mm^3 – 0 points, 15–25/mm^3 – 1 point, >25/mm^3 – 2 points); hemoglobin (>13 g/dL – 0 points, 11–13.5 g/dL – 1 point, <11 g/dL – 2 points); sodium (<135 mmol/L – 1 point); creatinine (>141/μmol/L – 2 points); and glucose (>10 mmol/L – 1 point). A total score of ≥6 is considered suspicious for the disease. While this may be true for the general population, the instrument must be used with caution and judiciously applied in the cancer population, which is replete with co-morbidities including chronic anemia, neutropenia, and renal insufficiency.

Plain films and CT scan classically show signs of gas in the soft tissue; however, gas tracking along fascial planes is only seen in 55% of CT scans. CT, however, will show asymmetric fascial thickening and fat stranding in 80% of cases [35]. A helpful bedside maneuver is the "finger test," whereby a 2-cm incision is made down to deep fascia and a gloved finger inserted to the base. A positive test is defined by dishwater pus, absence of skin bleeding, and lack of tissue resistance to blunt dissection [28]. The gold standard for diagnosis, however, remains fascial biopsy in the operating room.

Emergent surgery is required for any meaningful chance of survival. Prior to surgery, broad-spectrum antibiotics may be initiated to include coverage of streptococci, anaerobes, Gram-negative organisms, and Gram-positive bacilli [29]. More than 80% of cases are Type 1, defined as polymicrobial, whereas the remainder are Type 2 (Group A beta-hemolytic *Streptococcus* sp.) and Type 3 (marine *Vibrio* sp.) [28].

Other Soft Tissue Infections (Abscess, Bursitis, Tenosynovitis)

Unlike cellulitis, a deep tissue abscess is characterized by the presence of a purulent fluid-filled cavity, which can be documented by ultrasound, MRI, or CT scan. Drainage of the fluid, whether by aspiration, percutaneous drain placement, or surgery, is an essential aspect of treatment, since these infections typically do not resolve with antibiotics alone. It is important that fluid samples be obtained prior to initiation of antibiotics so that the organism can be isolated and tested for antibiotic susceptibility.

Synovial-lined spaces around tendons and bursa can potentially become infected and produce abscesses that need drainage or surgical debridement. Certain areas are especially prone to producing infected bursitis, including the olecranon and prepatellar bursas [36]. Although uncommon, flexor tenosynovitis in the hand is a true emergency that needs immediate attention, since this can result in rapid scarring and loss of function of the digit. The diagnosis is often made clinically based on examination and Kanavel's cardinal signs – flexion of the finger, fusiform swelling, tenderness along the flexor sheath, and pain with passive extension. Treatment is prompt surgical drainage, irrigation, and antibiotics [37].

Septic Arthritis

Septic arthritis can be defined as joint infection caused by pathogenic inoculation of the joint either directly or by hematogenous spread [38]. Risk factors for septic arthritis include presence of a prosthesis, intravenous drug use, alcoholism, diabetes, prior corticosteroid injection, and cutaneous ulcers. Immunosuppression resulting from chemotherapy or organ transplant can make patients particularly prone to septic arthritis [1].

A common proverb that underscores the urgency of septic arthritis is, "Time is cartilage." With time, bacterial toxins promote degradation of articular cartilage, mediated by proteolytic enzymes [1]. It is therefore imperative that it be diagnosed and treated in a timely manner, as irreversible joint damage and septicemia can even be seen in patients managed appropriately [38]. On physical exam, patients often are febrile with warmth and erythema about the joint with associated guarding. If the lower extremity is involved, they may have an antalgic gait. Patients tend to assume a position that minimizes pressure within the joint, which in the hip is a flexed, abducted, and externally rotated position, and in the knee or elbow is a slightly flexed position. It should be noted that in immunocompromised patients, fever and guarding may be diminished or absent [1].

Appropriate laboratory workup is critical. Initial labs should include CBC, CMP, ESR, and CRP. The gold standard for diagnosis of a septic joint is aspiration. This should be done after radiographs to evaluate for fracture or other pathologic processes. While the classic teaching is that synovial fluid with white cell count of >50,000 /mm^3 is synonymous with septic arthritis, this is an oversimplification. Coutlakis, et al. showed that a count of <50,000 was 5% sensitive, 50,000–100,000 was 47% sensitive, and >100,000 was 77% sensitive. In this study, crystalline arthropathies and rheumatoid arthritis accounted for 81% of patients with

white cell count in the 15,000–50,000 range, and 5/7 cases of septic arthritis with white cell count <20,000 grew atypical organisms [39]. Furthermore, patients with a polymorphonuclear (PMN) cell count of ≥90% are far more likely to have a septic joint than those <90% [40].

Antibiotics should be held until after joint aspiration in all medically stable patients. Following aspiration, initial antibiotics target common pathogens, with *S. aureus* and *Streptococcus* species accounting for more than 90% of cases [38]. That being said, atypical species such as Gram-negative organisms, *Mycobacterium,* and fungi can be seen in immunocompromised patients [1]. Antibiotics can be adjusted for susceptibilities and are typically continued for approximately 4–6 weeks [1]. Standard surgical care includes open or arthroscopic irrigation and debridement. In oncologic patients who are neutropenic or immunocompromised, alternatives include serial joint aspiration and bedside lavage.

Periprosthetic joint infections (PJIs) represent a different entity than septic arthritis of the native joint. However, timing remains critical. In acute infections, <4 weeks postoperatively, it may be possible to perform a surgical irrigation and debridement with modular component exchange (i.e., replacing easily removable parts such as plastic liners but leaving fixed hardware in place). In chronic infections, surgery entails removal of all components, insertion of an antibiotic spacer, an extended course of IV antibiotics, and a revision prosthesis.

On physical exam, PJIs can have similar findings to native septic joints. Additionally, there may be wound-related complications, such as dehiscence or drainage. However, PJIs sometimes show remarkably few signs, especially for chronic infections. While acute infections commonly show signs of rapid onset swelling, warmth and tenderness, chronic infections may be more subtle, with gradual, insidious pain, and no erythema or fever [41]. Radiographs are usually normal, but sometimes will show loosening of a previously well-fixed implant (especially if <5 years postoperative), subperiosteal elevation, or transcortical sinus tract [42]. Common risk factors include recent bacteremia, multiple prior surgeries, prior PJI, smoking, diabetes mellitus, cancer, inflammatory arthropathy, and immunosuppressive drugs [41, 42].

Laboratory cutoff values for PJI differ with respect to time. In patients who are <6 weeks postoperative, cutoffs are as follows: ESR has none, CRP >100 mg/L, synovial WBC count >10,000 cells/μL, PMN >90%. For patients >6 weeks postoperative, these values differ: ESR >30 mm/h, CRP >10 mg/L, synovial WBC count >3000 cells/μL, PMN >80% [42]. Diagnostic criteria are broken into major and minor. Major criteria include two positive cultures of the same organism or a sinus tract that communicates with the joint. Minor criteria include elevated CRP or D-dimer, elevated ESR, elevated synovial WBC, positive synovial alpha-defensin, elevated synovial PMN, and elevated synovial CRP. To confidently diagnose PJI, either 1 major or 6 minor criteria must be present [43].

Sinus tracts and open wounds should not be cultured in the ED, as they are more likely to grow colonized, nonpathogenic bacteria that confuse treatment goals. Following aspiration, empiric antibiotics should include MRSA coverage. In the uncommon scenario where the patient is unstable and septic, broad-spectrum antibiotics should be initiated prior to joint aspiration and blood cultures should be drawn [41].

Osteomyelitis

Osteomyelitis (OM) is defined as inflammation of the bone caused by an infecting organism [44]. Acute hematogenous OM is the most prevalent form. Patients typically present with fever and malaise. While WBC may be normal, inflammatory markers are usually elevated. Blood cultures should always be drawn, as the causative organism can be identified in approximately 50% of patients [44]. *S. aureus* accounts for the highest percentage of acute cases [45]. Radiographs often are unremarkable but can show soft tissue swelling after 1–3 days and periosteal elevation or bony destruction after 10–12 days [44]. MRI can be useful for diagnosis of OM and identification of associated abscesses. Empiric antibiotic coverage should include Gram-positive bacteria, Gram-negative bacteria, and potentially resistant organisms, depending on the patient's history [45]. The triad of fever, elevated CRP, and elevated absolute neutrophil count (ANC) correctly predicts methicillin-resistant *S. aureus* (MRSA) over methicillin-sensitive *S. aureus* (MSSA) in 87% of cases [46]. In leukemic patients, atypical bacteria or fungi have been isolated [47, 48]. Definitive treatment is with antibiotics. Some patients, particularly those with abscesses, may also require surgery.

Chronic OM is more indolent. Patients may have intermittent exacerbations over a course of years. Like acute cases, inflammatory markers are more sensitive than WBC count, which is elevated in only 35% of cases [44]. Those with chronic OM can have open wounds or sinus tracts communicating with deeper infection. It is not recommended to culture such wounds, as the isolates do not typically correlate with organisms that grow from an intraoperative bone biopsy [44]. In addition to X-rays, CT scan may help identify a sequestrum (infected, dead bone surrounded by new bone growth). Management requires a multidisciplinary approach, as the infection is typically difficult to eradicate, and associated comorbidities may preclude an aggressive debridement. Chronic OM can undergo malignant degeneration, most often as a squamous cell carcinoma (i.e., Marjolin ulcer) [49]. The latent period averages 27–30 years, with acute cases being very rare. Marjolin ulcers are characterized by drainage, foul odor, and a large, exophytic mass. Imaging should include X-rays, MRI, and a CT chest to evaluate for metastases. Diagnosis is confirmed by biopsy, and definitive treatment is wide excision or amputation [49].

Arthroplasty

Joint arthroplasty as a reconstructive modality has grown steadily with time. In years past, malignant primary bone tumors were routinely treated with amputation, but since the advent of effective chemotherapy, most sarcomas are now amenable to limb salvage [50]. The success of endoprosthetic reconstruction for primary bone sarcomas has led to its expanded use in benign and metastatic bone disease. While endoprostheses have consistently shown acceptable outcome in oncologic patients, the reported complication rates are 5–10 times higher than for routine, nononcologic joint arthroplasty [50].

Periprosthetic Fractures

Periprosthetic fractures are common but not always obvious since fractures may be minimally displaced. They are important to recognize early. The most significant negative prognostic indicator relating to early outcomes in periprosthetic hip fractures is delay to surgery [51]. The risk of periprosthetic fracture increases with chronic infection, poor bone quality, stress shielding, osteolysis, and oncologic resections [50, 52]. For oncologic patients, progression or relapse of disease in the bone surrounding the stem must be considered.

Common findings are pain, gross deformity, and swelling. A detailed exam of the entire extremity is important to rule out concomitant bony or neurovascular injury. Full-length orthogonal radiographs should always be obtained. Despite metallic streak artifacts, CT scans can be helpful when radiographs are equivocal.

The most common classification of periprosthetic hip fractures is the Vancouver classification: A (trochanteric), B (along the femoral stem, with 3 subtypes), and C (diaphyseal fracture distal to stem) (Fig. 33.4) [53]. Periprosthetic distal femur fractures are most commonly classified according to the Lewis and Rorabeck classification: I (nondisplaced fracture, intact prosthesis), II (displaced fracture, intact prosthesis), and III (loose or failing prosthesis) [54]. While these classification systems are designed for primary joints, the concepts of fracture location relative to the implant can be used for oncologic reconstructions as well [55].

Prosthetic Dislocation

The most common area for prosthetic dislocation is in the hip. In fact, dislocation accounts for >20% of revision hip surgery [56]. Dislocations can be attributed to one of three factors. Patient factors include older age, neurologic disease, cognitive impairment, spinal disease, and weak abductors [56, 57]. Implant factors include small head size and decreased offset. Surgeon factors include surgical approach (posterior approach most likely to dislocate) and component positioning.

Important details of the history include surgical approach, mechanism of dislocation, number of previous dislocations, and patient compliance with postoperative restrictions [58]. Location of surgical scars can serve as clues as to which approach was used. Posterior dislocations frequently occur when patients stand from a seated position. They result in an adducted, flexed, internally rotated, and shortened limb. Anterior dislocations result in abduction and external rota-

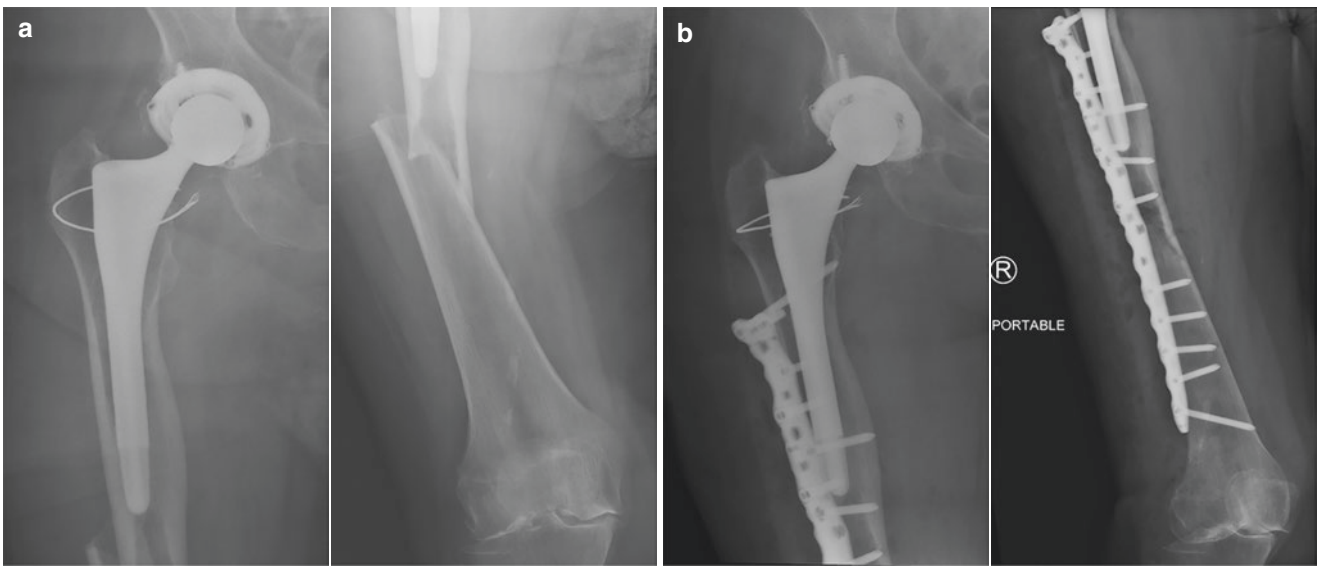

Fig. 33.4 (**a, b**) Preoperative and postoperative radiographs, respectively, of an 86-year-old female with multiple myeloma who sustained a pathologic periprosthetic femur fracture of the Vancouver C variety, for which she underwent open reduction with internal fixation

tion with either extension (pubic type) or flexion (obturator type) [58]. Evaluation of neurovascular status is important, as up to 10% of posterior dislocations can result in sciatic nerve palsy. Since infection can predispose to dislocation, laboratory workup should include a CBC, ESR, and CRP.

If an experienced emergency provider has adequate resources, a closed reduction may be attempted. While there are many techniques, the authors prefer the Waddell technique for posterior dislocations, whereby an assistant stabilizes the pelvis, and the provider straddles the patient's leg with the patient's hip and knee flexed, and exerts traction, with a combination of adduction and internal/external rotation [59]. Conscious sedation in the ED to reduce dislocated hips has been proven as a safe, effective method [60]. However, modular prostheses of the proximal femur in tumor patients have shown a re-dislocation rate following closed reduction of 58% compared to 11% of those that underwent an open reduction [61].

Complex arthroplasty for tumor patients is often performed with one of two methods to confer better stability: constrained liners or dual mobility systems. Constrained liners contain a metal ring to help stabilize the articulation between the head and the cup (Fig. 33.5). Dual mobility cups consist of a small metal/ceramic femoral head within a larger polyethylene head, which articulates with the acetabular component [58]. These are prone to what is called an intraprosthetic dislocation, whereby the polyethylene dissociates from the metal/ceramic head. While there are reports of successful closed reduction of dislocated constrained liners, it is typically recommended that the orthopedic surgeon perform open reduction of dislocations involving constrained liners or dual mobility cups [58, 62].

Pelvis

Patients with tumors of the bony pelvis and/or surrounding soft tissue represent a unique entity. The pelvis is the common pathway for all neurovascular structures supplying the lower extremities, genitalia, and perineum, thereby making surgery in this area complex and prone to complications. Hemipelvectomies performed for pelvic sarcomas are categorized by the area that is excised, but more broadly, are grouped as either internal (limb is preserved) or external (limb is amputated) [63]. One study showed a complication rate of 53% for external hemipelvectomies, most commonly due to wound infection and flap necrosis (Fig. 33.6) [64]. Other complications include ureteral injury, bladder fistula, strangulated incisional hernia, colocutaneous fistula, small bowel fistula, wound dehiscence, myocardial infarction, recurrent pulmonary emboli, and upper gastrointestinal bleed. In another study looking at both internal and external hemipelvectomies, wound infection occurred in 61.7% of cases [65]. Since these surgeries involve manipulation and/or reconstruction of large vessels, a possible dysvascular limb postoperatively should not be overlooked.

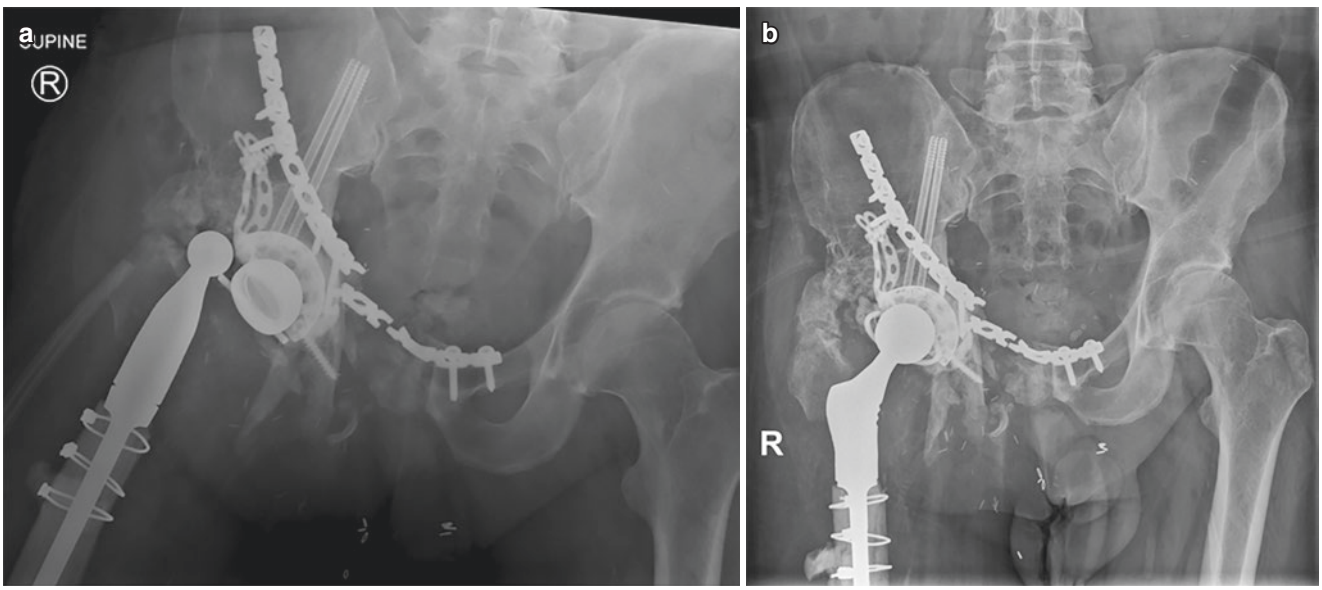

Fig. 33.5 A 53-year-old male with history of right pelvic chondrosarcoma 11 years status post internal hemipelvectomy and pelvic reconstruction with allograft prosthetic reconstruction with constrained liner total hip arthroplasty. Following a fall, the patient experienced a dislocation (**a**) that was revised to a new constrained liner in the operating room (**b**)

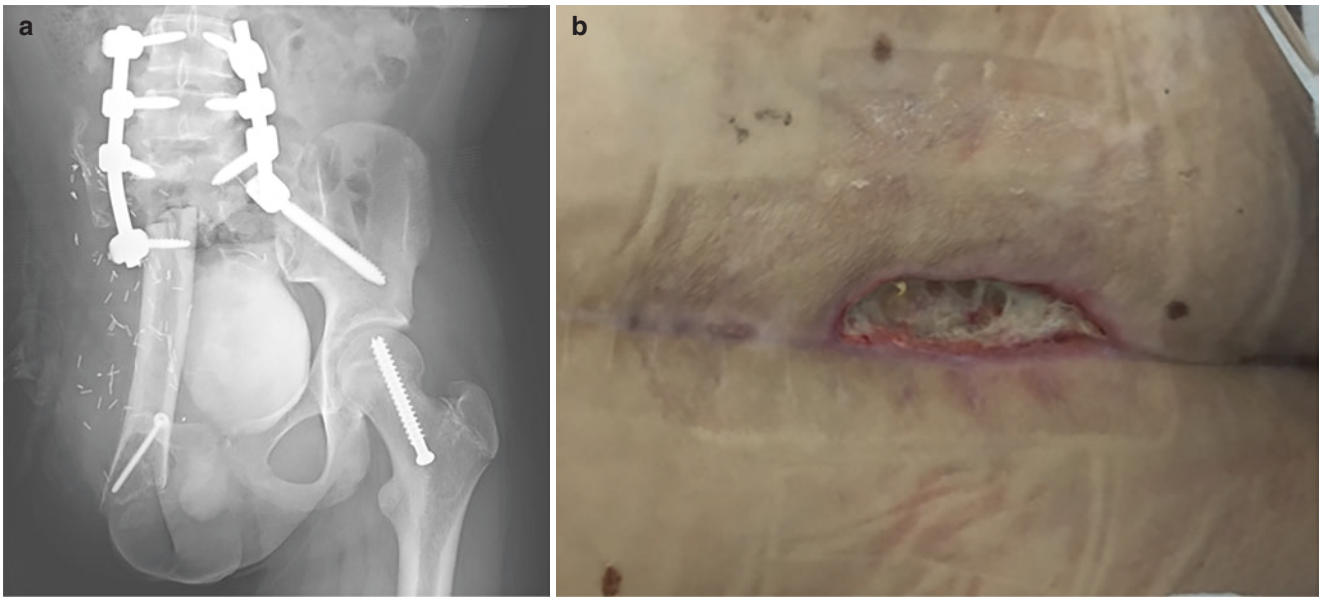

Fig. 33.6 A 15-year-old male who developed a radiation-induced pelvic osteosarcoma following treatment for neuroblastoma. He underwent a right external hemipelvectomy with reconstruction of the pelvic ring using the tibia of his amputated limb (**a**). Postoperatively, he developed a wound dehiscence and infection that required several months of antibiotics and wound care (**b**)

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Dermatology

34

Joanna Harp and Alina Markova

Case Study

A 70-year-old man with metastatic melanoma started on ipilimumab with nivolumab 11 days ago presents to the emergency department with a 6-day history of a painful rash and mucositis. He reports initial sores in the oral and ocular mucosa and subsequent development of pain with urination. He then developed a red painful rash that continued to spread over the next few days. He denies any other new medications and known allergies include sulfa medications.

On exam he is well-appearing with stable vital signs with widespread erythematous macules and papules on 50% of his body some with central duskiness that resemble targetoid lesions on <10% of his body. He has hemorrhagic crusts and ulceration of the lips and oropharynx, as well as conjunctival injection and periurethral erythema. With lateral pressure on the dusky areas of the rash, he develops shearing of skin.

Metabolic panel reveals normal electrolytes, serum bicarbonate of 23 mEq/L, glucose of 113 mg/dL, BUN of 30 mg/dL (H), creatinine of 1.1 mg/dL, albumin of 3.4 g/dL (L), AST of 172 U/L (H), and ALT of 199 U/L (H). Mycoplasma respiratory PCR and serum IgM and IgG are ordered. A punch biopsy is performed, revealing a lichenoid and subepidermal vesicular dermatitis with full-thickness epidermal necrosis.

The patient is diagnosed with Stevens-Johnson syndrome-like rash, CTCAE grade 3, due to ipilimumab/nivolumab. He is admitted to the intensive care unit and started on cyclosporine 2.5 mg/kg twice daily for 10 days and then tapered by 1 mg/kg/week, as well as topical cyclosporine drops to both eyes, dexamethasone swish and spit for his mouth, topical steroids to his glans, and Foley catheter. Denuded areas are covered with non-adhesive silver nylon dressings.

During his hospitalization, he does not have further fevers, but develops additional areas of denudation (<10% BSA). After day 5 of cyclosporine, he no longer develops new areas of rash, by day 15 his rash begins to hyperpigment, by day 22 his mucositis resolves, transaminases downtrend, and he is discharged.

Introduction

Patients with cancer can present with a wide range of common, serious, and at times life-threatening dermatologic conditions related to their underlying malignancy or to its treatment. Additionally, they may be at increased risk for infections, including cutaneous infections, secondary to immunosuppression. Recognition of the morphology of skin lesions (i.e., color, texture, shape, distribution, etc.) is an important step in the evaluation of these patients as it can greatly aid in formulating a differential diagnosis for various cutaneous manifestations. It is particularly crucial for emergency physicians caring for oncologic patients to be aware of cutaneous manifestations that herald severe and life-threatening conditions to allow for quick recognition and initiation of the appropriate treatment. This chapter discusses the clinical presentation, pathophysiology, diagnosis, and management of these severe conditions organized by morphologic presentation (Table 34.1).

Maculopapular Eruptions

The differential diagnosis for maculopapular eruptions includes drug eruptions, viral exanthems, and, in the appropriate patient population, graft-versus-host disease.

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Table 34.1 Cutaneous morphologies reviewed in this chapter

Maculopapular eruptions
Localized erythema
Generalized erythema (erythroderma)
Vesicles and pustules
Blistering diseases
Purpuric (non-blanching) eruptions

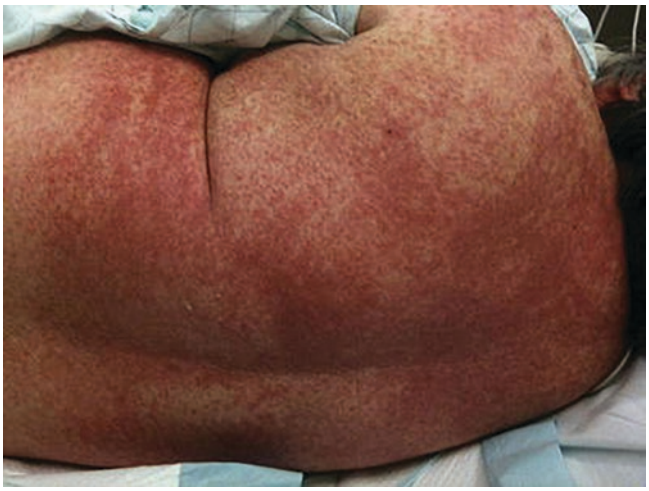

Fig. 34.1 Maculopapular eruption: diffuse erythematous macules and papules in a patient with DRESS secondary to allopurinol

Drug Eruptions

A maculopapular (exanthematous, morbilliform) rash (MPR) is the most common form of adverse drug reaction in hospitalized patients, occurring in 57% of patients with a drug eruption [1]. The eruption consists of erythematous macules and papules scattered diffusely over the body (often sparing the face) that may coalesce.

DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)/DIHS (Drug-Induced Hypersensitivity Syndromes)

Clinical Manifestations

When a maculopapular drug rash presents with fever, lymphadenopathy, or facial edema, drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) should be considered, and a work-up for systemic involvement should be performed. The cutaneous eruption is typically a MPR and rarely presents with purpura, vesicles, or pustules (Fig. 34.1). The liver is the most common site of visceral involvement, but other systemic findings include interstitial nephritis, pneumonitis, myocarditis, arthritis, cytopenias, atypical lymphocytosis, thyroiditis, and cerebritis. The clinical manifestations typically begin 2–6 weeks after initial exposure to the causative medication necessitating a drug history of the past several months when DRESS is suspected.

Pathophysiology/Etiology

DRESS is a delayed type IV hypersensitivity reaction that may involve impaired pharmacokinetics leading to the accumulation of drug metabolites. Genetic predisposition given the association with specific HLA alleles, viral reactivation, and the release of cytokines, including interleukin 5, may play a role [2]. Common etiologies include the anticonvulsants, sulfonamides, allopurinol, dapsone, and antiretroviral medications. A few anticancer drugs have also been associated including chlorambucil and lenalidomide.

Diagnosis

Diagnosis is made based on clinical findings of a MPR plus evidence of internal organ involvement, most commonly eosinophilia and transaminitis. However, any organ system may be involved, and eosinophilia is not required for diagnosis (thus the term drug-induced hypersensitivity syndrome (DIHS) is sometimes used). Biopsy findings are not specific for DRESS and show overlap features with simple drug eruptions.

Treatment

Early discontinuation of the suspected medication is necessary. Systemic corticosteroids (typically prednisone 1–2 mg/kg or equivalent) are the mainstay of treatment, and gradual taper with monitoring for flares is recommended to prevent relapse. The cutaneous and visceral manifestations may persist for weeks (rarely months), and patients should be monitored for late-onset thyroiditis and other autoimmune conditions.

Immune-Related Maculopapular Rash

Clinical Manifestations

Over 20% of patients treated with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or anti-programmed death 1 (PD-1)/programmed death ligand 1 (PDL-1) and up to 72% with anti-CTLA-4/anti-PD-1 combination therapy develop immune-related cutaneous adverse events (ircAEs), most commonly pruritus and MPR [3, 4]. These ircAEs may be associated with prolonged progression-free survival and overall survival [4]. Unlike MPR to traditional medications, those to immunotherapy may develop at any time during or months after completion of therapy, with a median onset of 62 days (range 1–1676 days) after initiation of therapy [4]. Cutaneous morphology of immune-related MPR may be indistinguishable from that due to traditional medications or have overlap with lichenoid, psoriasiform, or eczematous rashes. Maculopapular rash

severity is classified via the National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE) with Grade 1, macules/papules covering <10% body surface area (BSA); G2, macules/papules covering 10–30% BSA or rash >30% BSA with or without mild symptoms; and G3, macules/papules covering >30% BSA with moderate or severe symptoms [5]. Immune-related MPR with or without systemic involvement have a longer median duration of 37.5 days (range 1–700 days) than simple drug eruptions to traditional agents [6].

Pathophysiology/Etiology

Immune checkpoint inhibitors block CTLA-4, PD-1, and PDL-1 generating durable antitumor responses in several cancers [3]. Side effects of these agents may be attributed to a persistently stimulated immune system and are thus termed "immune-related adverse events" (irAE) [3]. Elevations in eosinophil counts, IL-6, IL-10, and IgE have been associated with grade 3 ircAEs, suggesting a pathogenic or correlative role, as well as potential targets for supportive care intervention.

Diagnosis

Diagnosis is made based on clinical findings of a MPR and history of current or prior immune checkpoint inhibitor (ICI) therapy. Biopsy findings are not specific for immune-related maculopapular rash and show overlap features with traditional drug eruptions.

Treatment

Goal of treatment of immune-related MPR is to minimize systemic immunosuppressive treatments while maintaining patient on current dose of ICI. Management of G1 MPR consists of high-potency topical corticosteroid twice daily [4]. For G2 MPR, systemic corticosteroids (prednisone 0.5–1 mg/kg) may be added [5]. For G3 or intolerable G2 MPR, ICI should be interrupted until MPR severity decreases to G0-1; and dose modified as per protocol; oral corticosteroids (prednisone 0.5–1 mg/kg) or biologics (infliximab, tocilizumab) are administered [3]. Patients should be reassessed every 2 weeks until improvement in grade. If reaction worsens or does not improve, dose reduction or discontinuation per protocol may be necessary. For corticosteroid-resistant MPR, check serum levels of IL-6 and TNF-α to assess for eligibility for targeted therapy (e.g., tocilizumab, infliximab) [4].

Viral Exanthems

Viral exanthems often present with a maculopapular eruption that can mimic drug eruptions. They are commonly seen in the pediatric population and immunocompromised adults who are at higher risk of viral infection and reactivation.

Clinical Manifestations

Although viral exanthems typically present with a MPR, they may also be scarlatiniform (diffuse small papules giving a sandpaper quality to the skin), petechial (non-blanching), or urticarial. Other clinical findings include fever, myalgias, arthralgias, nausea, vomiting, diarrhea, and malaise. SARS-CoV-2 infection can present with a variety of skin manifestations including MPR, macular erythema, urticaria, vesicles, livedo, and purpuric eruptions which tend to appear concurrently or after other viral symptoms [7].

Pathophysiology/Etiology

Causes of viral exanthems include Epstein-Barr virus, cytomegalovirus, enterovirus, adenovirus, human herpesvirus types 6 and 7, parvovirus B19, measles (rubeola), rubella, and early human immunodeficiency virus, among others. It is not known how viruses cause skin rashes, though it is likely related to immune system activation.

Diagnosis

It is not always possible to determine the exact viral cause; however, serologies, viral polymerase chain reaction assays, heterophile antibodies, and the presence of atypical lymphocytosis may be helpful. Skin biopsy may be useful in differentiating drug eruptions from viral exanthems; however, findings can be nonspecific.

Treatment

Viral exanthems are often self-limited with resolution after 1–2 weeks. Treatment includes symptom management and supportive care.

Graft-Versus-Host Disease (GVHD)

Acute graft-versus-host disease (GVHD) commonly appears as a diffuse MPR that classically presents in the early post-hematopoietic cell transplant period or after a reduction in immunosuppression (but can occur at any time after transplant). GVHD is most common after allogeneic hematopoietic stem cell transplant (alloHCT); however, it may be seen following autologous and solid organ transplant.

Clinical Manifestations

The skin is the most commonly affected organ in acute GVHD, presenting with a MPR. Individual lesions may be folliculocentric (centered upon a hair follicle) helping to distinguish from a drug or viral exanthem. A petechial component may be appreciated if the patient is thrombocytopenic. The liver and gastrointestinal systems are often also affected and, if severe, are associated with high morbidity and mortality. Chronic cutaneous GVHD has many clinical manifestations and can mimic lichen planus, lichen sclerosus, morphea,

and scleroderma. Engraftment syndrome presents around the time of neutrophil engraftment (ANC >500) with identical cutaneous manifestations as acute GVHD, as well as fever and evidence of capillary leak syndrome, and is more commonly seen after autologous transplant.

Pathophysiology/Etiology

In acute GVHD, alloHCT conditioning and damage to host tissues lead to the activation of host antigen-presenting cells. Donor T cells then proliferate in response to the activated antigen-presenting cells with subsequent activation of cytotoxic T lymphocytes and natural killer cells leading to tissue damage. Chronic GVHD is less well understood and is thought to involve donor T cells but also may involve B cells [8]. Risk factors associated with the development of GVHD include HLA incompatibility, unrelated donor, older age of recipient, peripheral blood stem cell source, and T-cell replete graft. In addition, the use of myeloablative-conditioning regimens is a specific risk factor for acute GVHD [9].

Diagnosis

The skin histology of acute GVHD shows varying degrees of keratinocyte necrosis, vacuolar changes at the dermal-epidermal junction, and a lymphohistiocytic infiltrate in the upper dermis, but a definitive diagnosis requires clinical correlation. The histology of chronic GVHD typically reflects the clinical pattern of the skin manifestations. Several serum biomarkers are also under active investigation to aid in the diagnosis of GVHD.

Treatment

Topical steroids are used to treat limited cutaneous acute GVHD; however, extensive cutaneous disease and other organ involvements often require systemic corticosteroids. Alternative and adjunct treatments for acute and chronic GVHD include phototherapy, other immunosuppressives including tacrolimus, mycophenolate mofetil, Janus kinase (JAK) inhibitors, Bruton tyrosine kinase inhibitors, and extracorporeal photopheresis among others.

Localized Erythema

Cellulitis

Cellulitis is a superficial, diffuse inflammation of the cutaneous dermis and subcutaneous fat secondary to an infectious process. Underlying immunosuppression and disruption of the skin barrier contribute to the development of cellulitis.

Table 34.2 Differential diagnosis for cellulitis in oncologic patients[a]

Deep venous thrombosis
Thrombophlebitis
Lymphangitis
Venous stasis dermatitis
Allergic contact dermatitis
Lipodermatosclerosis
Erythema nodosum
Sweet syndrome
Radiation dermatitis and radiation recall
Deeper infection
Necrotizing fasciitis[a]
Osteomyelitis
Abscess
Pyomyositis

[a]Expanded upon in text

Clinical Manifestations

Cellulitis presents with the acute onset of an erythematous, warm, tender plaque or plaques anywhere on the skin, usually over the lower extremities [10]. Cutaneous purpura may be present in the setting of thrombocytopenia or anticoagulation. Cutaneous edema can be severe leading to vesicle and blister formation. Cellulitis is almost always unilateral when located on an extremity. If findings are bilateral, an alternative diagnosis should be considered (Table 34.2). Patients are often afebrile, and increased white blood cell counts are seen in less than one-half of cases [10].

Pathophysiology

Cellulitis typically begins with organism entry through a disruption in the skin barrier especially in the setting of edema, trauma, ulceration, or a primary skin disorder, such as eczema or tinea pedis. The etiology is usually bacterial (most commonly *Streptococcus* genus followed by *Staphylococcus aureus*); however, cutaneous fungal infections including histoplasmosis and cryptococcosis can mimic bacterial cellulitis, especially in the immunocompromised host.

Diagnosis

Diagnosis is typically clinical. Skin biopsy is usually not helpful as histopathologic findings may be nonspecific, and tissue culture is positive for an organism in only about 20–30% of cases [10, 11]. However if cellulitis is worsening or not responding despite appropriate therapy, skin biopsy with tissue culture should be considered.

Treatment

Antibiotic therapy should be directed against streptococcal and staphylococcal organisms; however, broad-spectrum antibiotics including Gram-negative coverage are often warranted in the immunocompromised host. Adjunctive

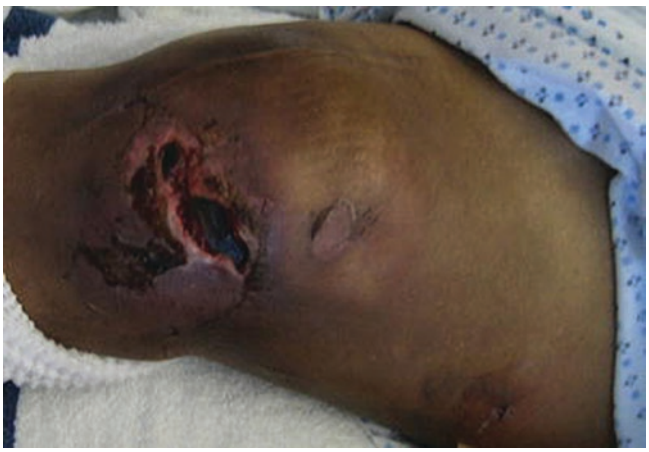

Fig. 34.2 Necrotizing fasciitis: rapidly expanding erythema, purpura, and necrosis secondary to a polymicrobial deep soft tissue infection on the right leg

treatments including elevation and compression in the case of an involved extremity and treatment of concomitant skin conditions that disrupt the skin barrier should be initiated.

The differential diagnosis of cellulitis includes early necrotizing fasciitis, a rapidly progressive bacterial infection with necrosis of the deep subcutaneous tissue and fascia. Early infection presents with erythema and edema similar to cellulitis (often with pain out of proportion to exam); however, this is often quickly followed by the development of non-blanching purpura and hemorrhagic bulla that can progress to necrosis and gangrene within hours (Fig. 34.2). The most common etiology is group A *Streptococcus* though infections are often polymicrobial. Diagnosis is often made clinically, but imaging may demonstrate fascial thickening or air within the soft tissues. Treatment is emergent surgical debridement and broad-spectrum antimicrobials.

Toxic Erythema of Chemotherapy

Toxic erythema of chemotherapy (TEC) describes a spectrum of cutaneous eruptions that are thought to occur secondary to the cytotoxic effects of chemotherapy on the skin and sweat glands. Many terms have been used to describe these eruptions, including acral erythema, palmoplantar erythrodysesthesia, hand-foot syndrome, eccrine squamous syringometaplasia, Ara-C ears, and neutrophilic eccrine hidradenitis [12]. Skin findings in TEC include symmetric, erythematous, and purpuric (non-blanching) patches, which can be associated with erosions, bullae, and desquamation (Fig. 34.3) frequently noted in intertriginous areas, genital, overlying joints, and acrally. Patients often describe burning or pruritus.

TEC has been attributed to cytarabine, doxorubicin, 5-fluorouracil, capecitabine, methotrexate, bleomycin, carboplatin, cisplatin, etoposide, gemcitabine, receptor tyrosine kinase inhibitors, cyclophosphamide, and melphalan, among others [12]. Diagnosis is often made clinically. TEC is typically self-limited, and treatment is largely supportive and includes topical steroids, analgesics, and emollients. Rarely systemic steroids are needed in severe cases. Prevention includes dose reduction and lengthening dose intervals.

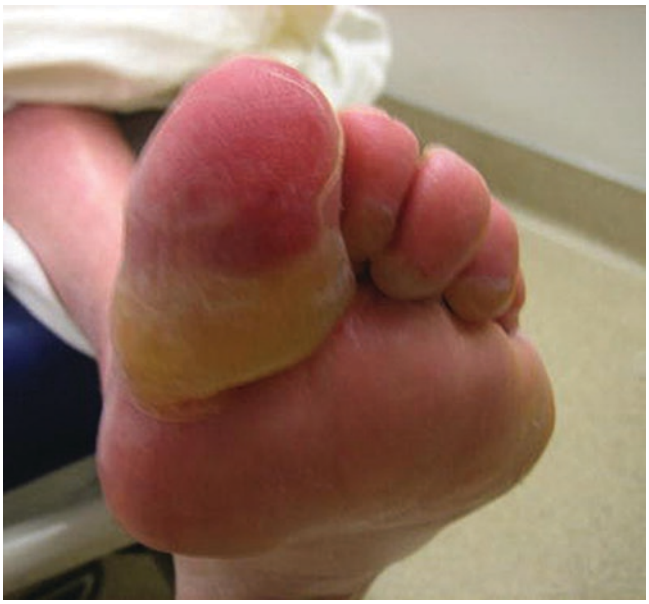

Fig. 34.3 Toxic erythema of chemotherapy: erythema and blisters secondary to sorafenib

Leukemia Cutis

Leukemia cutis is a skin eruption that results from cutaneous infiltration of malignant cells in the setting of leukemia, most commonly acute myeloid leukemia. Leukemia cutis classically presents with single or multiple raised red-purple (plum-colored) papules or nodules that can arise in any location [13]. Leukemia cutis may be the initial presenting manifestation of leukemia [14]. Skin biopsy should be performed to confirm the diagnosis and rule out clinical mimics including cutaneous infection and Sweet syndrome (acute febrile neutrophilic dermatosis). Management is aimed at treatment of the underlying leukemia. The development of leukemia cutis typically portends a poorer prognosis, with the exception of congenital leukemia with leukemia cutis [14].

Angioedema

Angioedema is the swelling of the deep dermis, subcutaneous, and submucosal tissues, most commonly on the eyelids, lips, and genitalia. It can involve the tongue and pharynx and, in such cases, become life-threatening.

Clinical Manifestations

The affected area is edematous and tender with the surface appearing normal or slightly pink. Angioedema can occur alone or simultaneously with hives. Patients with angioedema or hives must be monitored for signs and symptoms of anaphylaxis with evidence of respiratory compromise, hypotension, and shock.

Pathophysiology/Etiology

The etiology of angioedema is determined by the clinical manifestations and is critical for appropriate treatment. Angioedema that occurs with hives is due to an immediate type I hypersensitivity reaction mediated by IgE and mast cell degranulation. It can be triggered by infection, foods, and drugs or may be idiopathic. Angioedema that occurs without hives may be related to an inherited mutation or acquired in the presence of an underlying malignancy or autoimmune disorder. This pathway is driven by deficient or dysfunctional C1q esterase inhibitor, a critical enzyme in the complement and fibrinolytic cascade, leading to increased levels of bradykinin with resultant vasodilation and edema.

Diagnosis

Diagnosis of angioedema is often clinical; however, in the case of hereditary or acquired angioedema, low complement 4 (C4) level is seen both during and between attacks. C1q level is also low in acquired angioedema, helping to distinguish it from hereditary cases.

Treatment

Angioedema due to a type I hypersensitivity reaction may be treated with aggressive antihistamines and discontinuation of the offending agent if known. If there is concern for anaphylaxis, intramuscular or intravenous epinephrine should be used promptly. Recurring cases may require leukotriene receptor antagonists, immunosuppressants, and biologics [15].

Treatment for acute attacks in hereditary or acquired angioedema includes fresh frozen plasma, C1 inhibitor concentrate, kallikrein inhibitors, and bradykinin receptor antagonists [16].

Erythroderma

Erythroderma describes diffuse erythema of most if not the entire cutaneous surface often with exfoliative shedding of the skin. The differential diagnosis includes drug-induced, primary skin disorders, infectious etiologies, and paraneoplastic causes, among others (Table 34.3).

Table 34.3 Differential diagnosis for erythroderma

Drug-induced
Primary skin disorder
Psoriasis
Atopic dermatitis
Allergic contact dermatitis
Chronic actinic dermatitis
Pemphigus foliaceous
Infection
Toxic shock syndromes[a]
Generalized dermatophytosis
"Norwegian" crusted scabies
Viral exanthem
Neoplastic
Mycosis fungoides/Sézary syndrome[a]
Paraneoplastic phenomenon
Graft-versus-host disease
Others (rare): nutritional deficiencies, Kawasaki disease, cutaneous mastocytosis

[a]Expanded upon in text

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is an acute, life-threatening infection due to a toxin-producing strand of *Staphylococcus* or *Streptococcus*. Patients with underlying chronic medical conditions including cancer are at higher risk for TSS.

Clinical Manifestations

In both staphylococcal and streptococcal TSS, patients become acutely ill with high fever, hypotension, and evidence of multiorgan system involvement. Influenza-like symptoms including chills, myalgias, headache, vomiting, and diarrhea are common. Cutaneous findings are relatively nonspecific including subtle, diffuse, blanchable erythema as well as edema and erythema of the palms and soles followed by prominent desquamation within 1–2 weeks. Mucosal findings include conjunctival erythema, anogenital erythema, and a strawberry tongue.

Pathophysiology/Etiology

In TSS, specific strands of *Staphylococcus* and *Streptococcus* produce toxins that act as superantigens leading to a widespread T-cell activation and cytokine release that cause fever, capillary leakage, and hypotension. Staphylococcal TSS is most often associated with focal infections including surgical wound infections, burns, osteomyelitis, sinusitis, septic arthritis, and tampon use in menstruating women [17]. Streptococcal TSS is more often seen in connection with bacteremia, cellulitis, or necrotizing fasciitis [18].

Diagnosis

Both staphylococcal and streptococcal TSS have specific diagnostic criteria required for diagnosis (Tables 34.4 and 34.5).

Table 34.4 Diagnostic criteria for staphylococcal toxic shock syndrome

Fever
Hypotension
Diffuse erythroderma
Desquamation (1–2 weeks after illness onset)
Three or more of the following:
Renal dysfunction
Gastrointestinal: vomiting or diarrhea
Hepatic dysfunction
Hematologic dysfunction
Severe myalgias or elevated creatinine phosphokinase
Altered mental status
Mucous membranes erythema
Negative results of following tests, if obtained:
Blood, throat, or cerebrospinal fluid cultures for another pathogen
Serologic tests for Rocky Mountain spotted fever, leptospirosis, measles

Data from the Centers for Disease Control. Wharton et al. [60] and Centers for Disease Control and Prevention [61]

Table 34.5 Diagnostic criteria for streptococcal toxic shock syndrome

Isolation of group A *Streptococcus*
Hypotension
Two or more of the following:
Pulmonary dysfunction
Liver dysfunction
Renal dysfunction
Coagulopathy
Erythroderma of the skin
Soft tissue necrosis (e.g., necrotizing fasciitis)

Data from: The Working Group on Severe Streptococcal Infections. [62]

Positive blood cultures are more frequently seen in streptococcal TSS than in staphylococcal TSS.

Treatment

Treatment includes rapid introduction of intravenous antibiotics against *Staphylococcus* and *Streptococcus*. Clindamycin has direct antitoxin properties and has been shown to improve patient outcomes in TSS [19]. The source of infection should be investigated and may be occult. Intravenous immunoglobulin (IVIG) and corticosteroids may be beneficial in severe and refractory cases [20, 21].

Mycosis Fungoides and Sézary Syndrome

Mycosis fungoides (MF) and Sézary syndrome (SS) are types of cutaneous T-cell lymphoma (CTCL), and both can present with erythroderma. MF is a T-cell lymphoma with initial presentation in the skin but with potential involvement of the lymph nodes, blood, and internal organs. SS is a distinctive type of CTCL with leukemic involvement of malignant T cells.

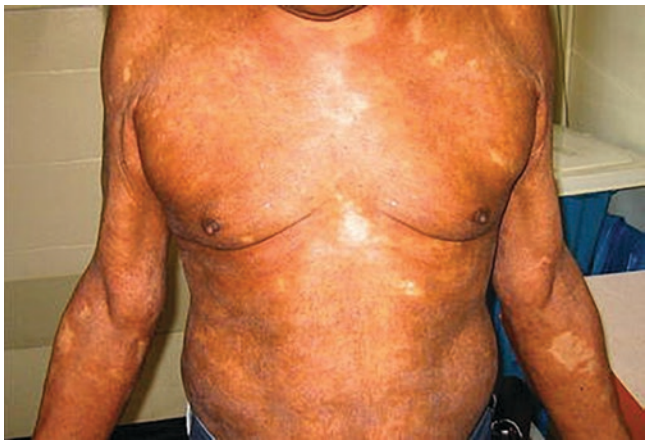

Fig. 34.4 Erythroderma: diffuse erythematous scaly plaques with small areas of sparing secondary to extensive mycosis fungoides

Clinical

MF typically presents with patches and plaques and may progress to tumors or erythroderma (Fig. 34.4). SS generally presents with erythroderma often in the setting of lymphadenopathy and indurated facial features from the infiltration of malignant cells [22].

Etiology

The etiology of cutaneous T-cell lymphoma is not entirely known. Hypotheses include chronic stimulation of circulating skin-homing lymphocyte subsets that cause transformation to a monoclonal population.

Diagnosis

Atypical lymphocytes within in the epidermis on skin biopsy are diagnostic of MF, though there may be overlap features with other chronic dermatoses. Diagnosis of SS requires the involvement of a clonal neoplastic T-cell population in the skin, lymph nodes, and blood.

Treatment

Patch stage MF may be treated with skin-targeted remedies such as topical steroids, topical nitrogen mustard, topical bexarotene, and phototherapy. Advanced MF presenting with erythroderma or systemic involvement and SS requires systemic therapies such as extracorporeal photopheresis, systemic retinoids, interferons, monoclonal antibodies, and chemotherapy regimens.

Table 34.6 Differential diagnosis for common causes of vesicular/pustular eruptions in oncologic patients

Drug
Acute generalized exanthematous pustulosis (AGEP)
Acneiform eruption secondary to epidermal growth factor receptor (EGFR) inhibitors
Steroid-induced acneiform eruption
Drug-induced autoimmune blistering disease (especially secondary to immunotherapy)
Inflammatory
Pustular psoriasis
Miliaria
Allergic/irritant contact dermatitis
Neutrophilic dermatoses
Infectious
Viral
Herpes simplex virus[a]
Varicella-zoster virus[a]
Coxsackie virus (hand, foot, and mouth disease)
SARS-CoV-2 (rare)
Bacterial
Bacterial folliculitis
Ecthyma[a]
Others: rickettsialpox, nocardiosis, listeriosis
Fungal
Disseminated candidiasis[a]
Disseminated opportunistic fungal infection
Atypical mycobacteria

[a]Expanded upon in text

Vesicles and Pustules

The differential diagnosis for vesicular and/or pustular eruptions in oncologic patients is broad and includes infectious causes, inflammatory disorders, and drug reactions (Table 34.6).

Drug-Induced Autoimmune Blistering Disease

Immune-Related Bullous Pemphigoid-Like Eruption

Clinical Manifestations

Immune-related bullous pemphigoid-like (irBP) eruption due to ICI occurs in 1–5% of patients treated with anti-PD1 or anti-CTLA-4 and may develop during or months after completion of ICI with a median 190–298.5 days (range 31–2380 days) after initiation of therapy [3, 4, 23]. Development of irBP is associated with improved tumor response after PD-1 therapy [24]. Cutaneous morphology of irBP may be indistinguishable from idiopathic BP. Bullous dermatitis severity is classified via CTCAE with G1, asymptomatic, blisters covering <10% BSA; G2, blisters covering 10–30% BSA, painful blisters, limiting instrumental ADL; G3, blisters covering >30% BSA, limiting self-care ADL; and G4, blisters covering >30% BSA, associated with fluid or electrolyte abnormalities, ICU care, or burn unit indicated [5]. Median duration of irBP is 97.5 days (range 13–390 days) [4].

Pathophysiology/Etiology

The exact pathomechanism of irBP is not yet established. In idiopathic (non-drug-related) bullous pemphigoid, BP180, a transmembrane glycoprotein in the skin, serves as an autoantigen targeted by antibodies leading to dermal-epidermal separation and blister formation. BP180 is expressed in melanoma and non-small cell lung cancer, possibly serving as the target of antitumor antibodies that may concurrently bind to cutaneous BP180 [23].

Diagnosis

Diagnosis is made based on clinical findings of a tense bullae or urticarial plaques and history of current or prior immune checkpoint inhibitor (ICI) therapy. Differential diagnosis for irBP includes linear IgA bullous dermatosis (LABD), bullous lichen planus, lichen planus pemphigoides, bullous erythema multiforme, and epidermolysis bullosa acquisita. Serologic testing by ELISA for circulating autoantibodies against BP180 and BP230 may be used to confirm diagnosis, correlate with disease severity, or monitor response to treatment. Histology will reveal a subepidermal bullous dermatitis with eosinophils, and direct immunofluorescence (DIF) shows linear deposition of IgG and C3 at the basement membrane zone of the dermoepidermal junction [3]. Histologic and direct immunofluorescence findings will not differentiate between irBP and idiopathic BP, but will distinguish from the aforementioned bullous conditions which may also be immunotherapy associated.

Treatment

Goal of treatment of immune-related BP is to minimize systemic immunosuppressive treatments while maintaining the patient on the current dose of ICI. Management of G1 irBP consists of high-potency topical corticosteroid twice daily [2]. For G2 irBP, hold ICI until severity decreases to grade 0–1, and add systemic corticosteroids (prednisone 0.5–1 mg/kg) [5]. For G ≥3 or intolerable G2 irBP, oral corticosteroids (prednisone 0.5–1 mg/kg) and rituximab (+/− IVIG [4]) are added [3]. Patients should be reassessed every 2 weeks until improvement in grade. If reaction worsens or does not improve, dose reduction or discontinuation per protocol may be necessary.

Viral Infections

Varicella-Zoster Virus

Varicella-zoster virus (VZV) from the *Herpesviridae* family is the cause of varicella (chickenpox) and zoster (shingles). Herpes zoster is a common infection seen in the oncologic patient.

Clinical Presentation

Varicella begins with mild fever, malaise, and myalgias followed by an eruption of 2–4 mm clear vesicles with a red rim. Over the course of several days, the vesicles become pustular and often form a prominent central hemorrhagic crust. Varicella in adults and immunocompromised patients may be associated with higher risk of morbidity and mortality, often with more extensive crusting and risk of internal organ involvement.

Herpes zoster is the reactivation of latent VZV. Zoster initially presents with a prodrome of burning, tingling, and pruritus followed by the development of grouped vesicles on an erythematous base in a dermatomal distribution. When certain dermatomes are affected, extracutaneous complications can occur including ocular complications, facial paralysis, loss of taste, deafness, and temporary inability to urinate or defecate. In the immunocompromised, pain and post-herpetic neuralgia may be more severe [25].

Disseminated zoster is defined as more than 20 vesicles outside the primary or contiguous dermatome (Fig. 34.5). Visceral involvement including pulmonary, hepatic, and central nervous system can occur in approximately 10% of immunocompromised patients [26].

Pathophysiology/Etiology

Varicella is transmitted through airborne droplets or direct contact with vesicular fluid. After varicella infection, the virus travels to the dorsal root ganglion where it remains latent until reactivation. It is the reactivation of latent VZV that causes zoster (shingles), which may occur spontaneously or in the setting of stress, fever, local trauma, immunosuppression, or radiation.

Diagnosis

The diagnosis can be made clinically based on typical lesional morphology. Polymerase chain reaction (PCR) from lesional fluid has become the preferred method for confirmatory testing based on higher sensitivity and rapid results (often within 24 h). If not available, a Tzanck smear or direct fluorescence antibody (DFA) assay or viral culture can be used [27].

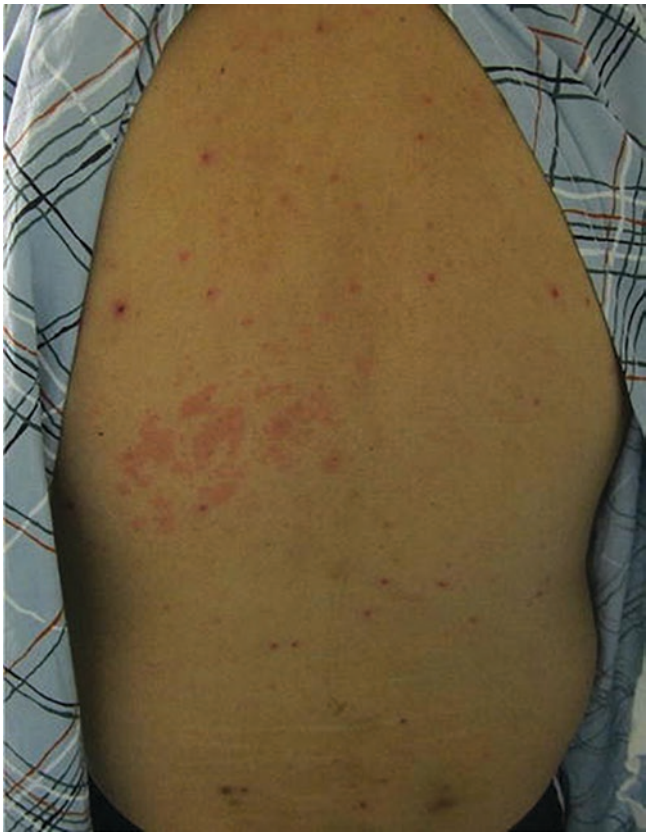

Fig. 34.5 Disseminated zoster: scattered vesicles on an erythematous base diffusely on the back with grouped vesicles in a dermatomal distribution on right mid-back

Treatment

Antivirals can be used for varicella and zoster in immunocompetent patients to decrease the duration and severity. Intravenous acyclovir is recommended for varicella in immunocompromised individuals and disseminated zoster. Postexposure prophylaxis with varicella-zoster immunoglobulin is recommended for immunocompromised individuals and nonimmune pregnant women.

Eczema Herpeticum (Kaposi's Varicelliform Eruption)

Eczema herpeticum is the cutaneous dissemination of herpes simplex virus (HSV) in areas of a preexisting dermatitis, such as atopic dermatitis (eczema), mycosis fungoides, or other skin conditions with impaired skin barrier.

Clinical Presentation

Eczema herpeticum appears clinically as discrete 2–3 mm punched-out erosions and circular hemorrhagic crusts con-

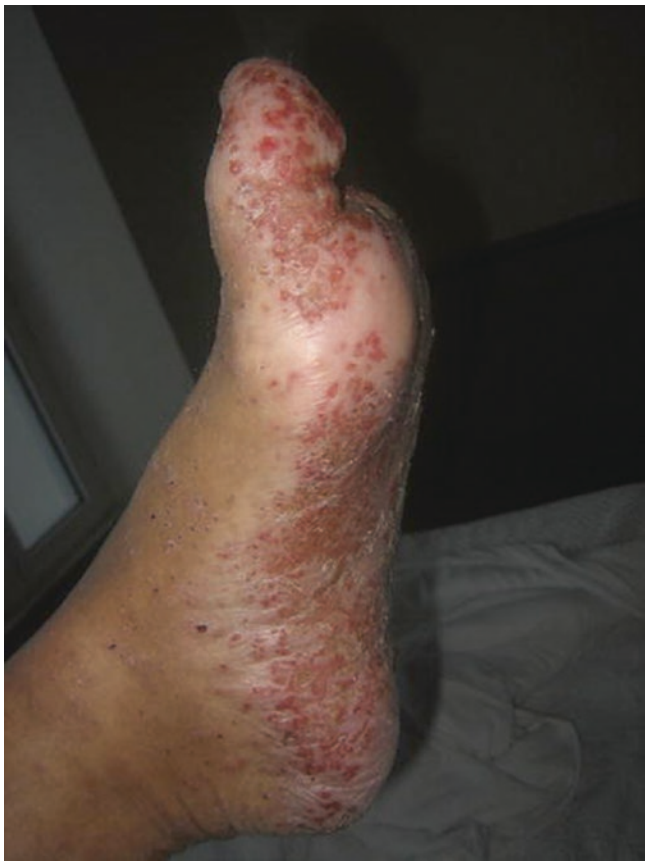

Fig. 34.6 Eczema herpeticum: diffuse 2–3 mm punched-out erosions within an area of eczema on the foot

centrated in areas of dermatitis (Fig. 34.6). Occasionally intact grouped vesicles or vesiculopustules may be seen, and the lesions may be superinfected with bacteria. Patients may have associated fever, malaise, and lymphadenopathy.

Pathophysiology/Etiology

Transmission of HSV1 is typically through direct contact with contaminated saliva, while HSV2 is transmitted through sexual contact. The virus then replicates at the site of infection and travels to the dorsal root ganglia, where it establishes latency until reactivation. Upon reactivation, the virus is able to spread via impaired skin leading to widespread involvement.

Diagnosis

As above, the preferred diagnostic technique is lesional PCR, though viral culture, DFA, and Tzanck smears may also be used.

Treatment

Treatment includes the use of antiviral therapy for 10–14 days, especially if immunocompromised, until all lesions are crusted over. Severe cases may require hospitalization with empiric intravenous acyclovir, while diagnostic studies are pending. Clinicians should also have a high suspicion for bacterial superinfection (especially with staphylococcal species) and low threshold to start concurrent antibiotics.

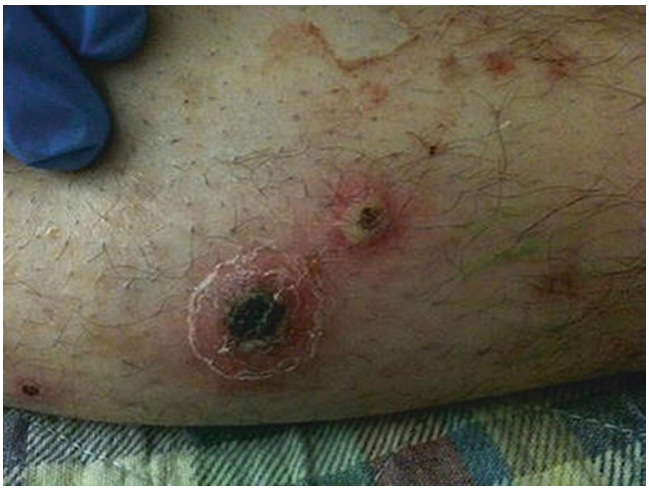

Fig. 34.7 Ecthyma: large pustules with central necrosis and crusting secondary to *S. aureus* bacteremia

Bacterial Infections

Ecthyma

Ecthyma is an ulcerative bacterial skin infection that can be localized or widespread with systemic manifestations. Ecthyma gangrenosum is a specific term for ecthyma skin lesions secondary to bacteremia with *Pseudomonas aeruginosa*.

Clinical Presentation

Ecthyma initially begins as single or multiple vesiculopustules that enlarge over several days. Lesions then ulcerate and develop central necrotic adherent crusts (Fig. 34.7). When multiple lesions are present, patients may have fever, chills, malaise, and, sometimes, hypotension and shock. Bacteremia should be strongly suspected.

Pathophysiology/Etiology

Ecthyma is secondary to a localized skin infection or secondary to bacteremia with cutaneous seeding. Ecthyma may be due to Gram-positive organisms including *Streptococcus* and *Staphylococcus* species and Gram-negative organisms such as *Pseudomonas*.

Diagnosis
The diagnosis can be made based on clinical appearance and Gram stain and culture of the purulent base. Skin biopsy and tissue culture can confirm the diagnosis and organism. Blood cultures should be ordered especially when multiple lesions are present.

Treatment
Treatment includes systemic antibiotics and wound care with soaking and gentle debridement of adherent crusts and topical antibiotic ointment. Hospitalization and intravenous antibiotics are indicated when multiple lesions are present or in immunocompromised patients.

Fungal Infections

Disseminated Candidiasis

Disseminated candidiasis is an infection most often seen in the immunocompromised host and can affect any organ system including the skin.

Clinical Manifestations
Cutaneous manifestations of disseminated candidiasis include pustules and scattered erythematous macules, papules, or nodules, often with a pale center. Other presentations include hemorrhagic bulla and purpura, especially in the setting of thrombocytopenia. Individuals are typically ill-appearing with tachycardia, hypotension, and fever.

Pathophysiology/Etiology
Candidal sepsis commonly occurs from *Candida* that has colonized the gastrointestinal tract or skin. *Candida albicans* is a common etiology of disseminated candidiasis, but *C. glabrata* and *C. tropicalis* can also be seen. *C. tropicalis* is more likely to produce cutaneous lesions and is common in patients with leukemia [28].

Diagnosis
Diagnosis can be established through skin biopsy and tissue culture or potassium hydroxide (KOH) preparation of purulent material. Budding yeast and pseudohyphae in the dermis are seen on skin biopsy. Evaluation also includes blood cultures, which may be negative, and evaluation for other organ involvement.

Treatment
In non-neutropenic patients, disseminated candidiasis can be treated with fluconazole. In neutropenic patients, amphotericin B, caspofungin, or voriconazole should be used. Any foci of infection such as lines and catheters should be removed.

Blistering Diseases

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous reactions that are typically triggered by medications. SJS/TEN may be more frequent in the oncologic population with one study showing a high incidence of TEN (6%) in bone marrow transplant patients, though cases of TEN-like acute graft-versus-host disease (GVHD) were included [29].

Clinical Manifestations
SJS/TEN typically presents 1–3 weeks after initiation of the offending medication with blisters centered on non-blanching macules or atypical target lesions characterized by two distinct zones: a dark red center surrounded by a pale red outer ring (Fig. 34.8). The majority of immune checkpoint inhibitor (ICI)-associated SJS/TEN-like reactions begin after the first or second infusion of ICI; however, it may occur even 140 days after initiation of therapy or after discontinuation [30, 31]. Lesions tend to start proximally on the trunk and face and then spread distally. Individual lesions can rapidly coalesce followed by cutaneous necrosis and epidermal sloughing that can become widespread. ICI-associated SJS/TEN-like reactions may be preceded by days to months of slowly evolving maculopapular, psoriasiform, or lichenoid

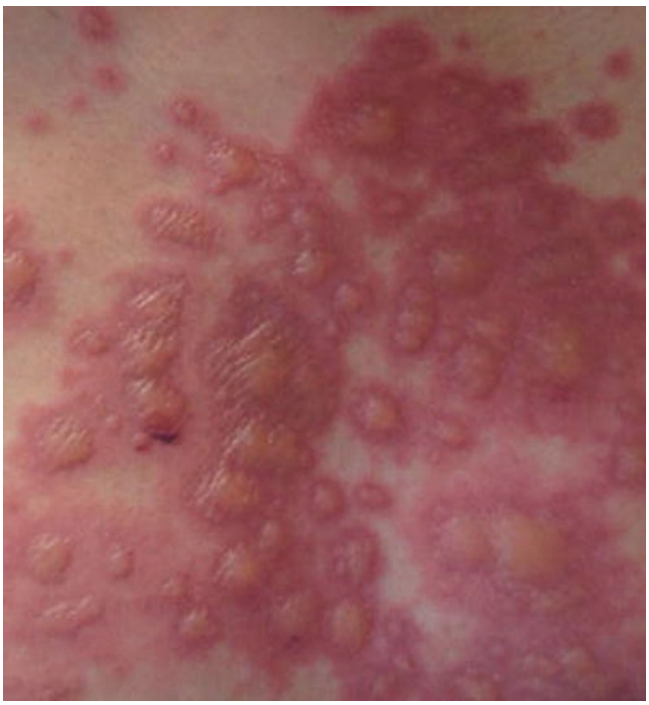

Fig. 34.8 SJS: coalescing blisters centered on non-blanching macules on the chest

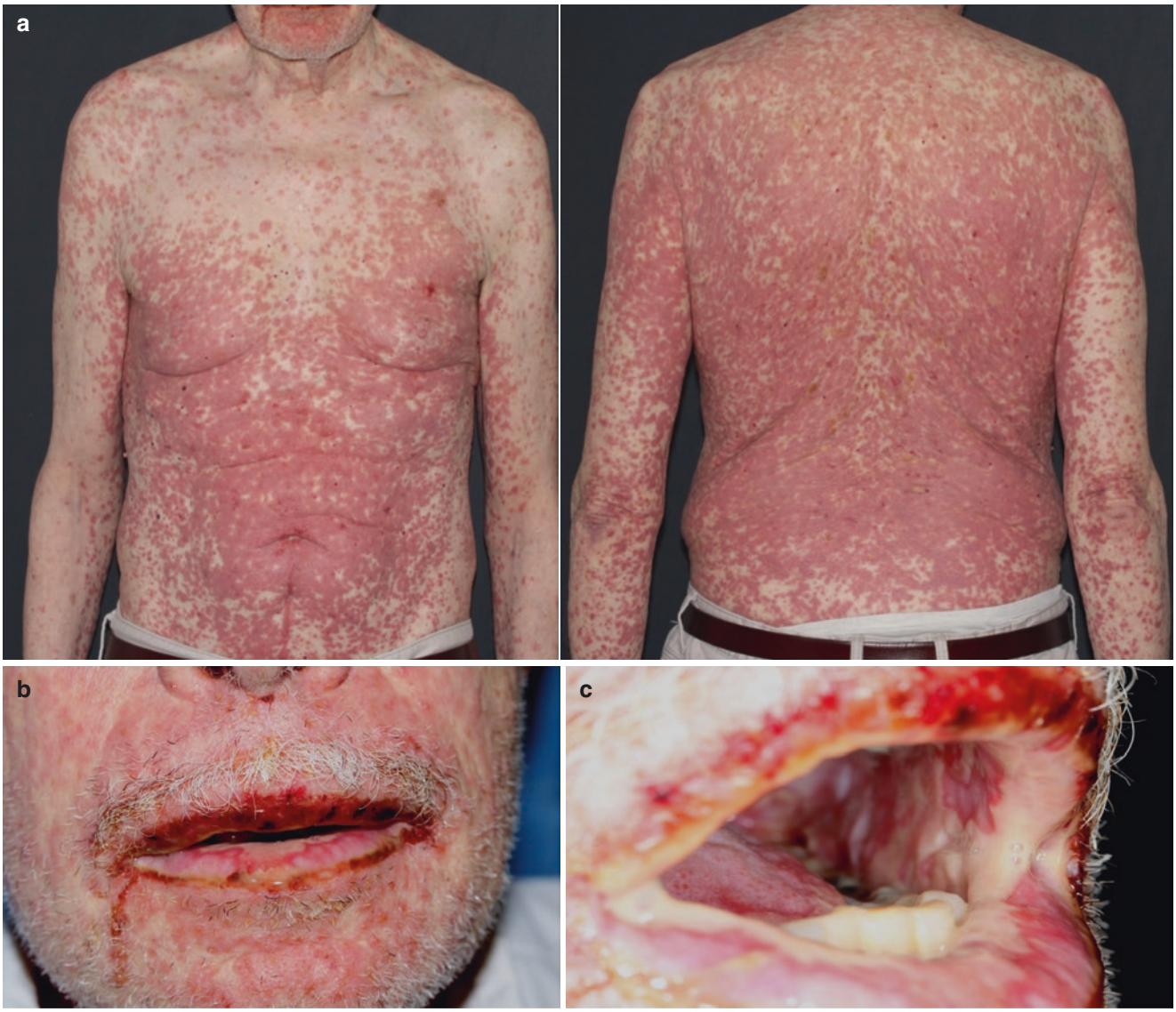

Fig. 34.9 (**a**) Generalized dusky red maculopapular eruption with scattered areas of erosions and hemorrhagic crusting, (**b**) cutaneous and mucosal lips with hemorrhagic mucositis, (**c**) confluent oral erosions with white fibrinous pseudomembranes

rashes, before developing denudation and mucosal involvement.

SJS/TEN exist on a spectrum defined by percentage body surface area (BSA) of epidermal detachment: SJS defined as <10% BSA, SJS/TEN as 10–30%, and TEN as >30%. ICI-associated SJS/TEN-like reactions severity is additionally graded via CTCAE starting with G3, skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment); G4, skin sloughing covering 10–30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment); and G5, death [5] (Fig. 34.9).

Erythema multiforme (EM) was previously considered by many to exist on the spectrum of SJS and TEN but has more recently been classified as a separate entity with distinctive skin findings and etiology and a good prognosis [32].

Typically multiple mucosal sites (oral, ocular, and/or anogenital) are involved with erosions, ulcerations, and hemorrhagic crusting [33] (Fig. 34.10). In severe cases, gastrointestinal (GI) and pulmonary involvement occur. Patients are often febrile and can display signs of shock. Associated organ system involvement is frequently reported including hepatitis, acute renal failure, myocarditis, and bone marrow suppression. One study found the mean adjusted mortality rates between 2009 and 2012 in the United States were 4.8% for SJS, 19.4% for SJS/TEN, and 14.8% for TEN [34].

A validated scoring system has been developed to assess the severity of illness and predict mortality in SJS/TEN

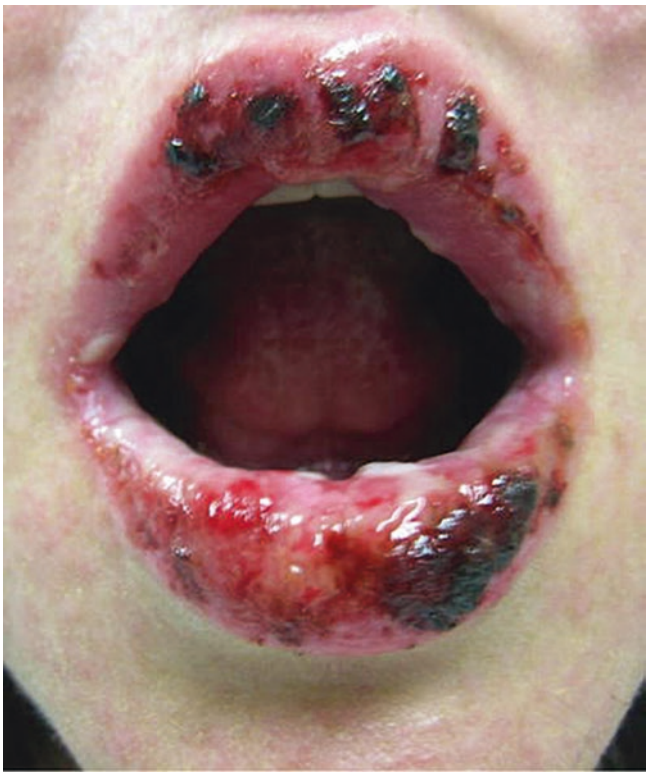

Fig. 34.10 Mucosal findings in SJS: erosions and hemorrhagic crusting

Table 34.7 SCORTEN severity of illness score in Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN)

One point for each of seven criteria if present on admission
Age >40 years
Presence of a malignancy (cancer)
Heart rate >120
Initial percentage of epidermal detachment >10%
Serum urea level >10 mmol/L
Serum glucose level >14 mmol/L
Serum bicarbonate level <20 mmol/L
SCORTEN predicted mortality rates
0–1: >3.2%
2: >12.1%
3: >35.3%
4: >58.3%
>=5: >90%

SCORTEN Score of toxic epidermal necrosis

(Table 34.7). However, with advances in wound care and treatment, the SCORe of Toxic Epidermal Necrosis (SCORTEN) may over-estimate mortality [35].

Pathophysiology

The pathophysiology of SJS/TEN is likely multifactorial involving cytotoxic T cells and soluble mediators including perforin, granzyme B, granulysin, and Fas-Fas ligand (FasL).

Table 34.8 Differential diagnosis for Stevens-johnson syndrome and toxic epidermal necrolysis (SJS/TEN)

Erythema multiforme[a]
Staphylococcal scalded skin syndrome
Pemphigus vulgaris/paraneoplastic pemphigus[a]
TEN-like acute graft-versus-host disease[a]
Linear IgA bullous dermatosis
Generalized bullous fixed drug eruption

[a]Expanded upon in text

Certain populations have specific human leukocyte antigen (HLA) types that are associated with a higher risk of development of SJS/TEN indicating a genetic component. Hundreds of medications have been associated with SJS/TEN, but the most common include allopurinol, aromatic anticonvulsants and lamotrigine, sulfa antibiotics, nevirapine, and nonsteroidal anti-inflammatory drugs (NSAIDs). In addition, many anticancer drugs have been associated with SJS/TEN including lenalidomide, thalidomide, docetaxel, and imatinib [36] and with SJS/TEN-like reactions including anti-CTLA-4, anti-PD-1, and anti-PDL-1 inhibitors [30]. The mechanism of SJS/TEN-like reactions is not yet established. Blockade of homeostatic PD-1/PD-L1 signaling, which maintains peripheral tolerance in the skin, may allow autoreactive CD8+ T cells targeting keratinocytes displaying self-antigens to become activated and proliferate leading to development of SJS/TEN-like reactions [37].

Diagnosis

Diagnosis can often be made clinically based on acute onset of blisters, targetoid (target-like) lesions, and epidermal detachment. Skin biopsy confirms the diagnosis and shows full-thickness epidermal necrosis. Where available, frozen sectioning of skin biopsy samples allows rapid diagnostic confirmation within hours. Direct immunofluorescence should also be done to rule out other etiologies of blistering disease, which is especially important for patients with history of ICI therapy given their predisposition for immunobullous disease (Table 34.8). SJS/TEN and ICI-associated SJS/TEN-like eruptions have overlapping histologic features.

Diagnosis may be more complicated in the setting of oncologic patients especially those who have undergone stem cell transplantation as severe acute GVHD can mimic SJS/TEN. Both diseases are at least partially mediated by cytotoxic T cells that target keratinocytes. Skin biopsies may be indistinguishable though the presence of eosinophils may be suggestive of GVHD.

Treatment

The most important interventions that have consistently been shown to improve survival in SJS/TEN is prompt

discontinuation of the offending medication and transfer to a burn unit, intensive care unit, or specialized care center. Supportive care consists of fluid and electrolyte balance, wound care, and monitoring for/early treatment of infection. An ophthalmology consult should be called whenever SJS/TEN is suspected. A urology and/or gynecology consult should also be considered. The use of prophylactic antibiotics is not recommended as no survival advantage has been shown [38].

A recent shift toward the use of cyclosporine and the tumor necrosis factor inhibitor etanercept has changed the landscape for treatment in patients with SJS/TEN. A 2018 meta-analysis of over 250 patients with SJS/TEN found that treatment with cyclosporine was associated with an approximately 70% decrease in mortality [39]. Typical recommended dose is 3 to 5 mg/kg/d divided bid for 7–10 days [39]. ICI-associated SJS/TEN-like eruptions may require longer therapeutic courses due to persistent immune activation and longer half-life of ICI when compared to traditional drug culprits. A 2018 randomized trial of 91 patients comparing etanercept versus systemic steroids showed improved clinical outcomes including decreased SCORTEN predicted mortality, decreased side effects, and more rapid re-epithelialization in the etanercept group [40]. While these results are encouraging, randomized, prospective trials are needed.

The use of systemic steroids in SJS/TEN (including recommended route of administration, dosage, and length of administration) remains controversial [35, 41–45]. While a recent 2017 meta-analysis [41] suggested decreased mortality rate, others have shown either no benefit or increased infection risk and length of hospital stay [35]. Some studies suggest a benefit especially if used earlier in the disease course, and at high dosages however, benefits must be weighed against increased infection risk and potential for delayed re-epithelialization [42, 43]. Intravenous immunoglobulin use in SJS/TEN is similarly controversial with some studies suggestive of benefit at higher dosages (over 2 gm/kg) [44], while a meta-analysis from the EuroSCAR group did not show survival benefit [45]. Despite this lack of clear supportive data, IVIG is still widely used for SJS/TEN in the United States [35]. Another important treatment consideration is the use of steroids and IVIG concurrently which also warrants additional study [35].

Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP) is an autoimmune mucocutaneous blistering disease associated with an underlying neoplasm. PNP has been described in association with lymphoproliferative neoplasms including chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and Castleman's disease, though solid organ tumors including thymomas have also been reported [46].

Clinical Manifestations

PNP is characterized by painful mucosal ulcerations and a polymorphous skin eruption with an associated neoplasm. Mucosal involvement typically affects the oral mucosa, especially the lips; however, the conjunctiva, anogenital region, nasopharynx, and esophagus may also be involved. Skin manifestations typically appear later and are varied including nonspecific erythematous papules, target-like lesions, and blisters. Internal organ involvement has also been reported including pulmonary (classically bronchiolitis obliterans), thyroid, renal, and gastrointestinal tract.

Pathophysiology

Autoantibodies against plakins (periplakin, envoplakin) are diagnostic of PNP. Plakins are important proteins found in hemidesmosomes and desmosomes, which serve as vital structures in keratinocyte adhesion to other keratinocytes and to the underlying basement membrane. In some cases, these autoantibodies have been shown to be produced directly by the associated neoplasm [47]. Additional autoantibodies involved in PNP are desmoplakins 1 and 2 and plectin.

Diagnosis

Currently no single established set of diagnostic criteria exists for PNP. Most proposed definitions include mucosal involvement, detection of autoantibodies via direct and/or indirect immunofluorescence antibody testing against envoplakin and/or periplakin, and the presence of an underlying neoplasm.

Treatment

PNP often improves after the removal or treatment of the underlying neoplasm. Rituximab is recommended as first-line treatment for PNP [48]. Other treatments including prednisone, cyclosporine, cyclophosphamide, and IVIG have also shown efficacy [46, 49].

Purpuric (Non-blanching) Eruptions

Purpuric eruptions describe non-blanching skin lesions secondary to hemorrhage into the skin. Purpuric lesions may be flat (macular purpura), small and raised (palpable purpura), or larger and netlike (retiform purpura). It is important to recognize the features of macular purpura, palpable purpura, and retiform purpura as the differential diagnosis varies based on these morphologic differences.

Table 34.9 Differential diagnosis for macular purpura

Platelet-related
Low platelets
Immune thrombocytopenic purpura (ITP)
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)
Disseminated intravascular coagulation (DIC)
Bone marrow failure
Drug-induced thrombocytopenia
Cirrhosis
Abnormal platelets
Congenital or hereditary platelet dysfunction
Nonsteroidal anti-inflammatory drugs
Renal disease
Thrombocytosis
Non-platelet-related
Trauma/Valsalva
Infections (Rocky Mountain spotted fever, parvovirus B19, disseminated strongyloidiasis)
Capillary fragility (actinic damage, Ehlers-Danlos syndrome)
Anticoagulant medications
Vitamin K deficiency
Vitamin C deficiency

Table 34.10 Differential diagnosis for palpable purpura (cutaneous small vessel vasculitis)

Inflammatory
Connective tissue disease-associated vasculitis
Mixed type II and III cryoglobulinemia
Henoch-Schonlein purpura (IgA vasculitis)
ANCA+ vasculitis
Infections (most commonly *Streptococcus*, HIV, hepatitis, tuberculosis)
Medications
Neoplastic (leukemic vasculitis, paraneoplastic phenomenon)
Idiopathic

Macular Purpura

Macular purpura describes flat areas of purpura of varying sizes. Lesions may be small (petechiae) or larger (ecchymoses). Macular purpura typically indicates hemorrhage into the skin secondary to low or dysfunctional platelets or vessel wall fragility in the absence of inflammation (Table 34.9).

Palpable Purpura

Palpable purpura describes small, raised, non-blanching lesions most commonly found on the lower extremities. Palpable purpura is the classic skin manifestation for cutaneous small vessel vasculitis (Table 34.10).

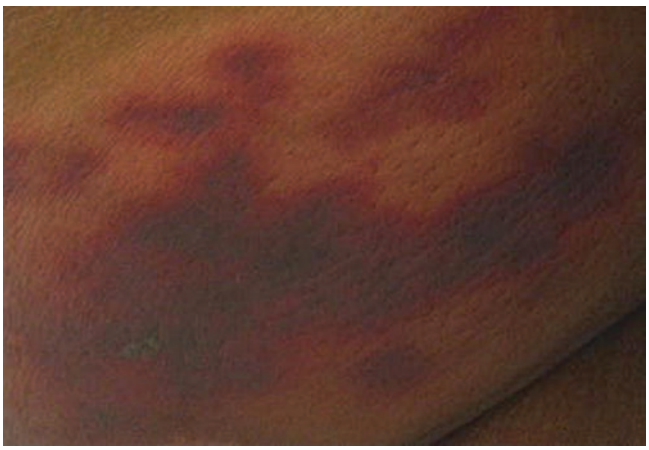

Fig. 34.11 Retiform purpura: netlike pattern of cutaneous purpura with central necrosis on the abdomen

Retiform Purpura

Retiform purpura describes cutaneous lesions that have a netlike or stellate (starlike) pattern of purpura often with central necrosis or ulceration, reflecting damage to larger vessels with resultant cutaneous ischemia and hemorrhage (Fig. 34.11). Damage to the vessel may occur through either infiltration of the vessel wall or occlusion of the vessel lumen (Table 34.11).

Acute Meningococcemia

Meningococcemia, a bloodstream infection with *Neisseria meningitidis*, is a rapidly progressive disease with a fatality rate of 7–11% [50]. Though its incidence is decreasing with increased vaccination in well-developed countries, its severity makes rapid recognition of paramount importance, especially in the immunocompromised host.

Clinical Manifestations

Acute infection results in a constellation of symptoms including high fever, myalgias, neck pain or stiffness, and headache. Skin findings typically manifest with a diffuse petechial rash that rapidly progresses to retiform purpura with a central "gun-metal gray" color and necrosis. Hypotension and shock may develop, and patients should be monitored for disseminated intravascular coagulation.

Pathophysiology/Etiology

Acute meningococcemia is caused by transmission via droplet of *Neisseria meningitidis*, a Gram-negative coccus. Disease typically develops 2 weeks after colonization of the pharyngeal mucosa. Cutaneous lesions of retiform purpura

Table 34.11 Differential diagnosis for retiform purpura

Vessel wall infiltration
Vasculitis
Septic vasculitis (bacterial, angioinvasive fungal)
Mixed type II and III cryoglobulinemia
Connective tissue disease-associated vasculitis
ANCA+ vasculitis
Leukemic vasculitis Polyarteritis nodosa Drug-induced vasculitis
Deposition (calciphylaxis, oxalosis)
Vessel lumen occlusion
Thrombotic
Abnormal coagulation
Hypercoagulable state (acquired or hereditary)
Warfarin-induced skin necrosis[a]
Disseminated intravascular coagulation/purpura fulminans
COVID-19-associated coagulopathy
Platelet plugging
Heparin-induced thrombocytopenia (HIT)[a]
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)
Paroxysmal nocturnal hemoglobinuria
Myeloproliferative disorders (essential thrombocytosis)
RBC occlusion (sickle cell, hereditary spherocytosis)
WBC occlusion (intravascular lymphoma)
Cold-related (type I cryoglobulinemia, cryofibrinogenemia)
Embolic: (septic, cholesterol, cardiac, air, fat emboli)

[a]Expanded upon in text

result from bacterial proliferation within the blood vessels creating vascular occlusion.

Diagnosis

Diagnosis of acute meningococcemia is clinical and should be suspected in any febrile patient with retiform purpura especially in the setting of headache and neck pain or stiffness. Treatment should be initiated prior to results of diagnostic testing to prevent rapid spread of infection. Cerebrospinal fluid (CSF) culture is superior to blood culture and positive in 90% of patients. PCR-based techniques on CSF approach a sensitivity of 100% [50]. Skin biopsy with tissue culture can be helpful to confirm the diagnosis.

Treatment

Neisseria meningitidis is highly sensitive to high-dose intravenous penicillin G, ceftriaxone, and cefotaxime, and treatment should be initiated within 1 h of presentation. Rifampin should be given to close contacts, and the vaccine is available for high-risk groups [51]. Adult oncologic patients are not routinely vaccinated unless a risk factor, such as previous splenectomy, is present.

Opportunistic Fungal Infections

Infections from the opportunistic dermatomycoses including aspergillosis, fusariosis, cryptococcosis, and zygomycosis can range from localized cutaneous infection to disseminated infection with multiorgan system involvement. Leukemia and lymphoma patients are most at risk for deep fungal infections when neutropenic.

Clinical Manifestations

Disseminated fungal infections can present with a wide range of cutaneous lesions including retiform purpura, papulonecrotic lesions, pustules, and hemorrhagic bulla [52]. *Cryptococcus* may present with umbilicated papules that resemble molluscum contagiosum. Patients are typically febrile and appear acutely ill.

Pathophysiology/Etiology

Systemic mycoses may begin with primary skin infection or spread to the skin from a distant site of infection. Disruption of skin barrier and mucosa from burns, trauma, and indwelling catheters, along with impaired immunity, are predisposing factors.

Diagnosis

Diagnosis can be established with skin biopsy, tissue culture, and microscopic examination of lesional fluid. Serum assays for components of the fungal cell wall, including 1,3-beta-D-glucan and galactomannan, can be used to screen for invasive fungal infection. Cryptococcal antigen is measurable in serum and correlates with fungal burden. Work-up should include chest X-ray and sputum culture to evaluate for pulmonary involvement.

Treatment

Expeditious treatment of deep fungal infection is key, and delay in treatment by as little as 2 h has shown to correlate with increasing mortality [53]. For many of the disseminated opportunistic mycoses, treatment is with intravenous amphotericin B. Voriconazole is first-line treatment for invasive aspergillosis. Prognosis is poor in disseminated disease but can be improved if neutropenia improves. Prophylactic treatment (agent of choice depends on the underlying malignancy, the length of expected neutropenia, etc.) may help reduce the risk of infection.

Anticoagulant-Induced Skin Necrosis

Anticoagulant-induced skin necrosis is a term that includes heparin-induced thrombocytopenia (HIT) and warfarin-induced skin necrosis (WISN).

Clinical Manifestations

Both HIT and WISN present with retiform purpura secondary to occlusion of cutaneous vessels. Necrosis may develop centrally secondary to tissue ischemia. HIT is most commonly found at sites of medication injection and typically develops within 5–10 days of starting heparin or within

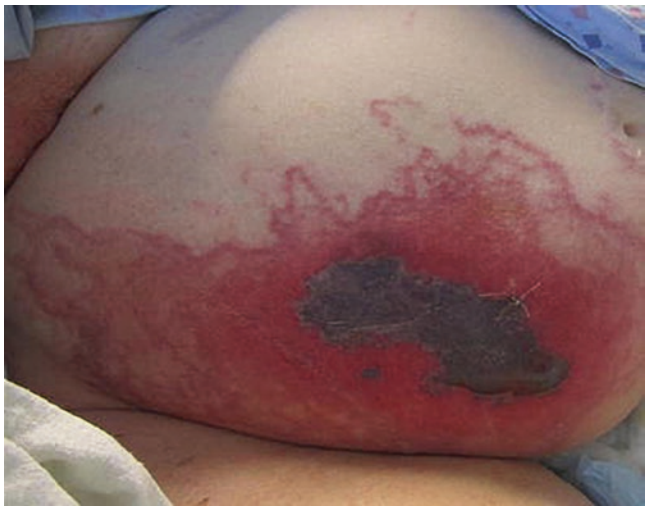

Fig. 34.12 Heparin-induced thrombocytopenia: retiform purpura with central necrosis at the site of heparin injection on the abdomen

24 h in patients with recent exposure to heparin (Fig. 34.12). WISN typically develops 3–5 days after beginning warfarin, often on fatty sites, such as breasts, thighs, buttocks, and hips, and is preceded by pain.

Pathophysiology/Etiology

In HIT, circulating antibodies develop that simultaneously bind heparin and platelet factor 4 (PF4) causing platelet activation and subsequent aggregation leading to venous and arterial occlusion. For reasons that are not entirely clear, low-molecular-weight heparins are less likely to cause platelet activation than unfractionated heparins [54].

Warfarin-induced skin necrosis results from the temporary imbalance in pro- and anticoagulant factors upon initiation of warfarin. Warfarin functions by inhibiting vitamin K-dependent coagulation factors. Protein C, an anticoagulant, is more rapidly inhibited by warfarin than procoagulant factors II, VII, IX, and X, leading to a temporary prothrombotic state. Risk factors include obesity, perimenopausal age, viral infection, and underlying hypercoagulable state.

Diagnosis

In both HIT and WISN, skin biopsies reveal a pauci-inflammatory thrombotic vasculopathy secondary to vessel occlusion. Subtle histologic variations in platelet thrombi (white clots) in HIT versus fibrin thrombi (red clots) in WISN can aid in differentiating the two histologically similar conditions [55]. In HIT, a rapid drop in platelets is typical resulting in absolute thrombocytopenia or a drop in platelets by at least 50%. The diagnosis of HIT can be confirmed with HIT antibody testing including immunoassays and functional assays. WISN is typically a clinical diagnosis that requires a compatible histology and history of recent initiation or reintroduction of warfarin. Patients may also have a history of an underlying hypercoagulable state or a recent infection. Protein C and S analyses are not sensitive or specific markers [56].

Treatment

Treatment of HIT consists of immediate discontinuation of heparin and supplementation with an alternative anticoagulant, such as fondaparinux, danaparoid, apixaban, rivaroxaban, or argatroban. Warfarin should be avoided initially but may be used once the patient has stabilized and platelet counts have recovered. Treatment of WISN involves immediate discontinuation of warfarin and administration of vitamin K and infusion of heparin at therapeutic doses. Fresh frozen plasma and protein C concentrate have been used to restore protein C levels and may be considered in the setting of life-threatening coagulation [56, 57]. It is recommended to bridge initiation of warfarin with heparin to avoid this phenomenon.

DIC/Purpura Fulminans

Infection, trauma, and malignancy among other insults can lead to imbalances in the coagulation system causing disseminated intravascular coagulation (DIC) with resultant simultaneous hemorrhage and thrombosis. If clotting is severe, purpura fulminans with acute, widespread retiform purpura and gangrene of the skin can develop.

Clinical Manifestations

DIC presents with skin findings indicative of simultaneous bleeding and thrombosis including petechiae, ecchymoses, and mucosal bleeding as well as lesions of retiform purpura. Purpura fulminans presents with rapidly progressive, widespread retiform purpura, hemorrhagic bulla, and symmetrical gangrene especially acrally (Fig. 34.13). Patients are acutely ill often with fever, shock, and evidence of multiorgan system involvement [58].

Pathophysiology/Etiology

Disseminated intravascular coagulation (DIC) and purpura fulminans are conditions in which systemic activation of coagulation leads to widespread clotting, particularly in small- and medium-sized vessels. Excessive clotting then leads to a consumptive coagulopathy where clotting factors cannot be generated as quickly as they are consumed and a bleeding diathesis ensues.

Diagnosis

Cardinal lab findings in DIC and purpura fulminans are consistent, independent of cause, and consist of thrombocytopenia, reduced plasma fibrinogen concentrations, and increased fibrin and fibrin products, with prolonged clotting times. Skin biopsy may aid in diagnosis and shows a thrombotic vasculopathy [58].

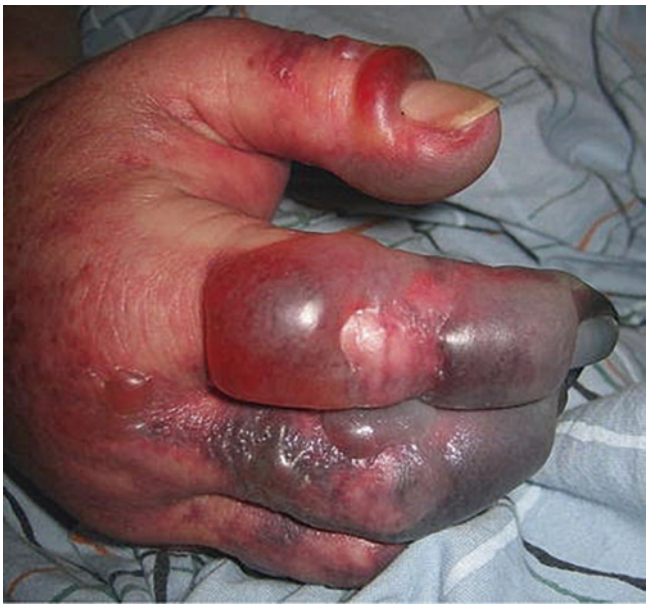

Fig. 34.13 Purpura fulminans: retiform purpura, blistering, and distal necrosis/gangrene of the hand

Treatment

Treatment of DIC includes treatment of the underlying cause and aggressive management of hemodynamic stability. If serious bleeding is present, platelet transfusions and administration of fresh frozen plasma or cryoprecipitate may be indicated. The use of heparin is typically limited to patients with chronic, compensated DIC that have predominantly thrombotic manifestations. Protein C concentrate may be considered in cases of DIC secondary to hereditary or acquired protein C deficiency or in cases of purpura fulminans. Adjunctive hyperbaric oxygen and surgical debridement with skin grafting may prove beneficial in patients with extensive skin necrosis and gangrene [59].

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Pediatrics

35

Kathleen M. Stephanos and Lindsey Picard

Introduction

Oncologic emergencies in pediatrics can be subdivided into presentation of disease and treatment of disease-associated emergencies. Each of these areas poses distinct risks and complications for the patient. This chapter will attempt to cover a multitude of different cancerous processes as well as their presentations. While many complications are similar to those in adults, the pathophysiology and resulting types of cancer can result in different treatment plans and prognostics. Many therapies are similar to those used in adults, with known adverse reactions, but their impact on the pediatric patient may result in more severe or long-term effects, a scenario which may become more common as cancer survivorship continues to improve.

Case Study

A 7-year-old female presents with 1 month of intermittent fevers, body aches, and left forearm pain. She has been seen by several providers since the onset of symptoms and diagnosed with viral illnesses. On the day of presentation, her parents described her as less alert throughout the day, so they brought her to the emergency department (ED). She has a temperature of 38.4, a heart rate of 130, a blood pressure of 85/50, a respiratory rate of 30, and an oxygen saturation of 100% on room air. On exam, she appears listless, with dry mucous membranes, her cardiopulmonary exam is normal other than the aforementioned vital signs, and she has diffuse lymphadenopathy and hepatosplenomegaly. What are the concerns for this patient? What is the differential diagnosis? What is the initial management?

The child in the case presents initially with symptoms suggestive of acute leukemia. Symptoms supportive of this are her hepatosplenomegaly, intermittent fevers, and changes in mental status. Acute mental status changes may signify that this patient is experiencing CNS involvement of her illness or that she has hyperleukocytosis causing hyperviscosity symptoms. It is important to recognize this as a pediatric emergency that will require admission to a pediatric hospital with oncologic coverage. Unlike adults, who (if not in a blast crisis or having other requirements for admission) can often be managed as an outpatient, children are often admitted for initial oncologic evaluation.

Two months later, she returns with 1 hour of fever. She has been on chemotherapy since her primary presentation. She was tolerating her treatment well, other than occasional nausea and vomiting, until the day of presentation when she developed abdominal pain and has not been able to eat or drink. When the fever occurred, she was instructed by her oncologist to come directly to the ED. On arrival, her temperature is 39.2, heart rate 120, blood pressure 90/55, and respiratory rate 22, and she has an oxygen saturation of 99% on room air. On exam she appears uncomfortable and has red cracked lips and a dry tongue. Her cardiopulmonary exam is notable only for the aforementioned vital signs. On abdominal exam, her hepatosplenomegaly has resolved, but she now has right lower quadrant tenderness with rebound and guarding. What is on the differential for this patient? What is the management?

On her return visit, there are many factors to consider; however, the most pressing are recognition of the possibility of both neutropenic fever and typhlitis, both of which can be rapidly fatal if not identified early. This patient requires prompt recognition and should not be in a waiting room for any duration of time. Other considerations include possible mucositis with dehydration or bowel perforation. She may also have appendicitis or even intussusception based on her pain. Her immunosuppressed state may have delayed the common symptoms of these, and her medications may have mimicked some of these symptoms as well causing family

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and providers to attribute her recent nausea and vomiting due to medication effects rather than early signs of disease. Based on her presentation, intravenous fluid should be started, with antibiotics and imaging for better assessment of her abdomen.

History and Background

Overall incidence of pediatric cancer has not changed significantly over the past several decades; however, there has been one drastic change: on average, more than four out of every five children diagnosed with cancer can be expected to survive. A particular challenge of pediatric cancer is the small number of cases, resulting in limited testing and evaluation of new treatment options [1]. Pediatric cancers are managed several ways including multidisciplinary therapeutic strategies such as surgical intervention, cytotoxic chemotherapy, radiation therapy, and autologous as well as allogeneic bone marrow or stem cell transplants. More recent studies have begun to evaluate the efficacy of monoclonal antibody therapy, though this is not a commonly used therapy at the time of this publication [2, 3]. The treatment options are cancer specific, but nearly all pediatric cancers acquire some form of significant immunosuppression.

Anatomy

As with all oncologic processes, pediatric cancers are due to an unregulated overgrowth of mutated cells. The most common sites for this in children are bone marrow and central nervous system—specifically intracranial [4]. Therapy, therefore, targets these cells specifically.

Pathophysiology

New Onset

There are a variety of different pathophysiologic pathways depending on the type of pediatric cancer. In many pediatric cancers, the different hematopoietic cell lines are affected, which in turn leads to anemia, leukocytosis, and thrombocytopenia. A normocytic, normochromic anemia results from bone marrow infiltration (seen in leukemia), as an inflammatory process from cytokine release resulting in decreased production or from direct blood loss [5]. Similar effects are seen on platelets. Hyperleukocytosis can be seen in different pediatric cancers, defined as white blood cell count above 100,000 cells/mm^3. It can result in leukostasis leading to pulmonary and CNS complications [5].

Tumor lysis is another feature of cancer pathophysiology. It can occur as a result of high tumor burden and cell turnover or from initial treatment. It leads to the release of intracellular components into the blood, including DNA and electrolytes. Multiple electrolyte abnormalities are seen in tumor lysis syndrome. Renal failure, cardiac dysrhythmias, and seizures can result [6].

Undergoing Therapy

Treatment of disease targets the rapidly dividing mutated cells in order to prevent their further growth. This has known consequences on the surrounding cells, as well as other highly replicative cells within the human body including hair, blood, and mucosal, among others. Many chemotherapeutic agents result in severe, but often anticipated, adverse side effects. Common sequelae include alopecia, mucositis, vomiting, and diarrhea, accompanied by malnutrition. Often, these complications are managed in an outpatient setting. For example, prevention of emesis with 5-HT3 antagonists is common practice [7]. Pediatric infusion centers can administer intravenous fluids and prescribe antiemetics. For more severe emesis episodes, a child may require admission or presentation to an emergency department for management of hydration [8]. Immediately following initiation of chemotherapy, a patient may develop tumor lysis syndrome, as mentioned above. In known oncologic patients, this is typically seen on initiation of therapy only, during which the patient is already admitted and being monitored and would be an unanticipated finding in an ED. Beyond these anticipated outcomes, many of the current chemotherapeutic agents have severe impacts on organs throughout the body, some which are temporary and others that are more permanent [8].

Epidemiology

Pediatric cancers are the second most common cause of death due to disease in children and adolescents, behind only accidents. In 2018, there were over 10,000 new cancer diagnoses in children under age 14. Leukemias are the most common cancer diagnosis, followed by central nervous system (CNS) malignancies in young children. Adolescents have a different distribution; CNS cancers and lymphomas are the most common forms found in this age group [4].

Health Economics

A pediatric cancer admission costs roughly $40,000, which is five times more expensive than an average general pediatric hospital admission [9]. In addition to the medical costs from hospital admissions, cancer treatments, and outpatient follow-ups, many families experience increased financial

burdens as parents commonly experience employment disruptions [9]. A recent study demonstrated that advanced childhood cancer takes a disproportionate toll on family finances when compared to other complex chronic pediatric patients [10]. In one study, nearly 45% of families of pediatric patients had an identifiable socioeconomic or resource limitation hardship [11]. All of these contextual factors are important for the ED provider to appreciate for this patient cohort.

Presentation/Diagnosis

New Onset

Many initial cancer presentations in the pediatric population are nonspecific. Typically they present with vague symptoms, such as fatigue, headache, pallor, weight loss, unexplained bone pain, or fevers [12]. In young children, any unexplained weight loss is concerning, since children normally will follow a progressive growth curve. Even those children attempting to become less obese will target limiting weight gain rather than overt weight loss unless under specific guidance or weight loss planning. There are some more specific presentations to be aware of; for example, new-onset wheezing, particularly in school-aged children, can indicate a mediastinal mass [13]. Altered mental status, focal neurologic deficits, and seizures without return to baseline could be secondary to an intracranial malignancy [12]. This can also be due to spread of a hematologic malignancy or hyperleukocytosis. Metastatic brain lesions are an exceptionally uncommon presentation of disease in children, which is notably different than in adults. Unexplained bruising, bleeding, or petechiae are suggestive of thrombocytopenia, which could be from a malignant process. Intermittent abdominal pain, vomiting, constipation, or bloody stools could indicate intra-abdominal cancer pathology. Neuroblastoma may cause catecholamine-induced hypertension with cardiomyopathy or parasympathetic-driven refractory diarrhea, a-traumatic "raccoon eyes," or abnormal movements [14]. Superior vena cava syndrome may occur in children, though is less common than in adults, and can be due to thrombus or mass compression. This presents with cough, dyspnea, and swelling or color changes to the head and neck [6]. Tumor lysis may be found at presentation due to solid organ tumors. This is due to tumor involution and breakdown due to the tumor overgrowing its vascular supply, at which time tumor cells may rapidly break down, releasing electrolytes into the bloodstream. As the kidneys attempt to filter these lysed cells, renal function decreases, and the patient may suffer acute renal failure. Likewise, the released electrolytes, most specifically potassium and phosphorus, can have significant cardiac and other systemic effects [6] (Table 35.1).

Table 35.1 Common pediatric cancers and the symptoms associated with their diagnoses

Cancer	Symptoms
Leukemia, lymphoma	Fever, bone pain, bruising, bleeding, lymphadenopathy
Mediastinal masses	Wheezing, cough
Neuroblastoma	Diarrhea, hypertension, constipation, abdominal pain, periorbital ecchymosis, cardiomyopathy
Abdominal masses	Constipation, abdominal pain, vomiting, bloody stools
Intracranial masses	Altered mental status, seizures, neurologic deficits, headache, vomiting

Undergoing Therapy

There are a wide variety of complications due to cancer treatment. Surgical interventions may cause typical postsurgical issues including bleeding, pain, or infection. Medical treatments, however, may have systemic effects posing risks to nearly every organ system.

Blood dyscrasias are one of the most common side effects of chemotherapeutic agents and are typically the result of bone marrow suppression. These include leukopenia, thrombocytopenia, and anemia. Specifically, neutropenia may be severe resulting in increased risks for viral, bacterial, and fungal infections [15]. In these patients, fever can be the first sign of a severe systemic infection, which can, in turn, result in rapid and severe decompensation, particularly if not recognized and managed quickly [15]. Due to immunosuppression, patients may not show typical early signs of infection, including pain. Additionally, symptoms of infection may be mistaken for other common medication side effects, such as fatigue or pallor. Neutropenic fever comprised about 19% of post-diagnosis ED presentations in one study, and infections (or signs and symptoms of infection) accounted for over 40% of all visits [8].

Anemia may be the result of increased bleeding or bone marrow suppression [16]. Bleeding is commonly due to thrombocytopenia, though can also be due to coagulopathic side effects of medications [5]. Most oncologic patients have treatment-specific target transfusion criteria, though it is important to recognize that the need for frequent transfusions poses a risk for iron overload [12, 17].

While there is much focus on the bone marrow suppressive implications for the hematopoietic system, there is also a risk of hypercoagulation. Overall pulmonary embolism is very rare in children, but it has an incidence of 2% on routine CT (not specifically looking for pulmonary embolism) in oncologic patients. This hypercoagulopathic side effect also increases the risk of stroke, superior vena cava syndrome, as well as other ischemic diseases [12]. Thrombosis may also be related to indwelling central lines [16].

Hemoptysis may develop due to easy bleeding as a result of low platelets, pulmonary embolism, pulmonary edema, or, very commonly, infection. Diffuse alveolar hemorrhage may also occur and is associated with hematopoietic stem cell transplant [14]. This is also found in 40% of pediatric cancer autopsies and is the most frequently missed diagnosis in pediatric cancer deaths [18].

Cardiovascular compromise secondary to treatment may present early or be delayed. Pericardial effusion and cardiac tamponade may present, similar to adults, with chest pain, respiratory symptoms (such as cough or dyspnea), tachycardia, and occasionally pulsus paradoxus [19]. Specific therapies (e.g., anthracyclines) may also cause arrhythmias as well as heart failure resulting in long-term cardiac effects [20].

In the gastrointestinal tract, one of the most frequent side effects of cancer treatment is mucositis [16]. This is due to the breakdown of mucosal tissue throughout the intestinal tract, which is painful and increases the risk of bleeding, infection, and dehydration [21]. Bowel perforation may be found on presentation or due to treatment of disease. Steroids as well as chemotherapeutic agents increase the propensity for perforation due to structural effects on the bowel [21]. Patients may present with minimal initial symptoms due to immunosuppression. One of the most severe intra-abdominal complications of chemotherapy is neutropenic enterocolitis (also called typhlitis or ileocecal syndrome). This life-threatening disease process typically presents in severely neutropenic patients and is often associated with leukemia or lymphoma. Patients report abdominal pain, which is commonly located along the colon and often in the right lower quadrant. They may also have fever or diarrhea [22]. It is believed that this is due to chemotherapy causing friable mucosa vulnerable to infectious infiltration [22].

Pancreatitis can be caused by a variety of therapeutic agents including corticosteroids, trimethoprim-sulfamethoxazole (to prevent immunosuppression-related pneumocystis pneumonia), asparaginase, mercaptopurine, and cytarabine [14].

Renal system injuries are categorized as subacute and acute. Subacute injury is often due to treatment modalities and is less likely to present in extremis to the ED, as these patients are closely monitored for blood dyscrasias and electrolyte abnormalities during treatment [23]. Acutely, renal injury may occur due to tumor lysis syndrome. Hemorrhagic cystitis is a common complication of chemotherapy, specifically cyclophosphamide [24].

Graft-versus-host disease can cause a myriad of symptoms throughout the entire body. This typically occurs following allogeneic bone marrow transplantation. Symptoms may include skin findings, dyspnea, myalgias, fatigue, fever, liver disease, and other gastrointestinal effects [14].

Electrolyte abnormalities are also possible with a variety of chemotherapeutic agents (Table 35.2) [25–38]. Specifically vincristine, cyclophosphamide, and cisplatin are associated with syndrome of inappropriate anti-diuretic hormone (SIADH), resulting in hyponatremia [16].

Table 35.2 A review of common severe side effects for patients on various chemotherapeutic agents

Medication	Life-threatening complications
Asparaginase	Hemorrhage, coagulopathy (thrombosis, emboli) hypotension, pancreatitis, bronchospasm, decreased blood counts
Busulfan, myleran	Thrombosis, electrolyte abnormalities, severe fatigue, renal damage, decreased blood counts
Carboplatin	Renal damage, decreased blood counts, electrolyte abnormalities, bone marrow suppression
Cisplatin	Decreased blood counts, allergy, renal damage, electrolyte abnormalities, peripheral neuropathy
Cyclophosphamide	Bladder damage (hemorrhagic cystitis), oral sores, infertility
Cytarabine	Decreased blood counts, fever, flu-like symptoms, aseptic meningitis, neurotoxicity, intestinal necrosis, toxic megacolon, pancreatitis, rhabdomyolysis
Daunorubicin, doxorubicin	Decreased blood counts, heart failure, arrhythmias (note also changes in the color of sweat and urine)
Etoposide	Hypotension, peripheral neuropathy
Hydroxyurea	Decreased blood cell counts (macrocytosis, neutropenia), infection, severe central nervous system disease, thrombosis
Mercaptopurine	Decreased blood counts, fever, pancreatitis, renal toxicity, mucositis, pulmonary fibrosis
Methotrexate	Decreased blood counts, diabetes, intestinal perforation, dizziness, headache, focal neurologic findings, rashes, infertility, severe renal disease, intestinal bleeding, mucositis, tumor lysis syndrome, obstructive and restrictive lung diseases
Thioguanine	Decreased blood counts, portal hypertension, liver failure
Thiotepa	Intracranial hemorrhage, seizure, mucositis, decreased blood counts, infertility, asthma
Topotecan	Myalgias, decreased blood counts, dyspnea
Vincristine	Nerve injuries (central and peripheral), ischemic heart disease, decreased blood counts, intestinal perforation and necrosis, decreased blood counts. Hepatic sinusoidal obstruction

This list excludes common symptoms that are unlike to present to an emergency department or require significant intervention—such as nausea and vomiting [25–38]

Evaluation

New Onset

Given the typical, vague initial presentation for pediatric cancers, there is no set ED protocol for evaluation of these patients. Work-up should be based on history and physical

examination. Laboratory studies may include complete blood count with differential, electrolytes, renal function, lactate dehydrogenase, and uric acid. Imaging may be indicated, such as chest x-ray, head CT or MRI, abdominal ultrasound, or extremity imaging. Consultation with hematology/oncologic colleagues will help guide additional laboratory and imaging studies.

When there is concern for tumor lysis syndrome, lab work should focus on electrolytes, as well as lactate dehydrogenase, uric acid, calcium, and phosphate [6]. Elevated potassium, phosphate, urea nitrogen, uric acid, and lactate dehydrogenase, accompanied by low calcium, are supportive of this diagnosis [6].

Undergoing Therapy

Each therapeutic tool has different, treatment-specific risks. Radiation therapy typically causes local inflammatory reactions. While nearly all chemotherapeutic medications can result in decreased blood counts due to bone marrow suppression, as well as nausea, vomiting, anorexia, or alopecia, some have more severe complications specifically associated with their use. (See Table 35.2 for high-risk complications associated with specific medications.) Asking the patient or family member to identify the medications may help the provider assess for the risk for specific diagnoses.

In general, patients with oncologic processes who are undergoing treatment require rapid ED assessment and prompt placement in a treatment room isolated from other patients and more specifically from patients with infectious symptoms [39]. These oncologic patients typically warrant blood work including complete blood counts with differential, allowing assessment for neutropenia, anemia, and thrombocytopenia. Absolute neutrophil count should be determined using the following formula: (percent neutrophils + percent bands) × white blood cells × 100 [40]. A neutrophil count below 1000 cells/mm^3 is considered neutropenic, and below 500 cells/mm^3, severely neutropenic [4]. A basic metabolic panel assesses hydration and electrolyte status. Finally, liver function testing and pancreatic tests, specifically lipase, are often warranted in patients with nonspecific infection symptoms and should be obtained in patients with any gastrointestinal symptoms [16]. The emergency physician should communicate with the patient's oncologist or a member of their team early in evaluation and management to ensure appropriate medications and treatments are given and risk factors are identified. Infectious evaluation of pediatric patients should include complete blood counts, cultures (including cultures from any central access points), urinalysis, and urine culture. If there is concern for neutropenia, urine should not be obtained via catheter due to the risk for introduction of infection. Concern for meningitis may require meningitic dosing of antibiotics and avoidance of lumbar puncture in a thrombocytopenic patient [15].

Diffuse alveolar hemorrhage may manifest as bilateral opacities on chest x-ray or ground-glass opacities on CT. Chest radiographs may reveal cardiogenic pulmonary edema and cardiomegaly [14]. For pulmonary embolism, CT angiography is the test of choice. MRA, while having some utility in adult patients, has not been assessed for pediatrics and therefore has an unclear role. Nuclear medicine or interventional radiology studies are rarely utilized in children [14].

If there is concern for pericardial effusion and/or tamponade, chest x-ray may reveal a water-bottle heart appearance; though this has some specificity, its sensitivity is poor [12]. Echocardiography is the test of choice to evaluate pericardial effusion.

Plain abdominal radiographs may find thickened bowel walls or air-fluid levels, suggesting graft-versus-host disease, typhlitis, or other intra-abdominal pathology. Ultrasound may also be utilized in pediatric patients to assess bowel wall thickness, with levels over 3 mm suggestive of thickening [14]. Ultrasound avoids radiation and allows more accurate measurement of bowel wall thickness than CT. Pneumatosis intestinalis indicating typhlitis may be seen on a screening x-ray, but CT should be performed as well, assuming the patient is stable enough for transport.

Patients with pancreatitis do not necessarily require emergent imaging; however, ultrasound is the evaluation of choice. Again, radiation is limited, and an enlarged or hypoechoic pancreas, including pseudocysts, may be seen. For patients in whom ultrasound is equivocal or unavailable, CT scan is an appropriate modality for assessment [14]. Of course, pediatric cancer patients may have typical diseases of childhood (e.g., appendicitis, intussusception) and should have standard of care performed for these diagnoses as well.

Management

New Onset

The management of new cancer diagnoses in the ED is most frequently supportive. As mentioned above, consultation with pediatric hematology and oncologic is important. Their expertise will guide the emergency physician through the necessary primary evaluation. Initial presentations can include tumor lysis and hyperleukocytosis, both of which are treated initially with intravenous fluids. Allopurinol and rasburicase can be added as needed to treat tumor lysis [6]. Hyperleukocytosis may require leukapheresis and high volume intravenous fluids [12]. These additional medications should only be added when discussed with pediatric hematology and oncologic.

Patients with mediastinal masses with concern for airway compression may require intubation. These patients also highlight the importance of imaging for new wheezing. Management should not include steroids as this can impact the tissue and limit the ability to make an accurate diagnosis on biopsy.

Neuroblastoma patients may require blood pressure management, when experiencing blood pressure elevations above the 95th percentile for age and height or if it is associated with end-organ dysfunction.

A key component to the initial management of a new cancer diagnosis is the discussion with the patient and their family. Discussing the diagnosis first with the parents is vital as it allows the parents to cope with this life-changing news. In addition, it allows for the parents and physician to consider the most appropriate way to tell the patient. The patient should be informed using age-appropriate terminology. A child life specialist may assist in this discussion with the patient and family when one is available. Ideally, children who are old enough to understand would be informed of the diagnosis shortly after parents are notified. There is evidence that delays in informing children can result in distrust of both parents and the medical system [41].

Undergoing Therapy

Patients presenting with isolated blood dyscrasias may require transfusion to meet the goals of their therapeutic plan. Blood should be irradiated and leukocyte reduced [17]. Additionally, cytomegalovirus (CMV) is less common in pediatric than adult patients, and CMV-negative blood products should be administered unless there is documentation that the patient has tested positive for CMV antibodies [5]. Transfusions in pediatrics are typically administered based on weight, 10 ml/kg up to 250–300 ml (the typical adult unit of blood), and can be expected to raise hemoglobin levels by 2–3 g/dL [16].

Coagulopathy resulting in increased clot burden may require anticoagulants. This must be done cautiously in order to avoid bleeding and worsening anemia [5].

Fever in the setting of known or possible neutropenia is considered an emergency, and these patients require prompt antibiotic therapy. While ampicillin-sulbactam and cefepime are often cited as the antibiotics of choice, therapy should be tailored to the patient's past sensitivity and resistance patterns when possible [15, 16]. If this information is not readily available to the emergency provider, the patient's oncologist should be consulted. In ill-appearing patients, the addition of vancomycin should be added to management early in treatment [15].

Pericardial effusion may require placement of a pericardial drain or surgical intervention with a pericardial window [19]. In cases of tamponade physiology with cardiovascular collapse, emergent pericardiocentesis may be indicated [29].

Pancreatitis is treated similarly in children as in adults, with initiation of intravenous fluids and bowel rest [42]. Intra-abdominal processes such as typhlitis or graft-versus-host disease require the initiation of antibiotics and surgical consultation [22].

Electrolyte repletion should be monitored closely and based on the severity of the imbalance [16].

Of note, the specific diagnosis of COVID-19 has not been shown to have significant morbidity and mortality in pediatric oncologic patients to date, though understanding of this disease and its impact on this patient population is actively changing [43].

Disposition/Follow-Up

New Onset

Unlike the adult population, new cancer diagnoses in pediatric patients typically require hospital admission. During the admission, thorough work-up of the new cancer will occur with discussions of management options. Depending on the cancer type, initiation of treatment may occur during this admission. Coordination of care is key during the admission to facilitate accurate diagnosis and treatment, as well as provide the necessary patient and family support.

Undergoing Therapy

The majority of pediatric patients who present to an ED while undergoing chemotherapy will require hospital admission [8]. Some exceptions include those who require simple transfusions or patients with concern for neutropenic fever who both appear well and are not found to have neutropenia. Disposition of all patients with treatment-associated complications should be in conjunction with the patient's primary oncologic team.

Prognosis/Treatment

Over 80% of children will pass the 5-year survivor mark. In a 2020 review by Horn et al., the overall mortality rate of pediatric patients with a cancer diagnosis was estimated to be 23% with 73% of deaths resulting from their primary cancer and 27% from a competing cause [44]. Deaths from competing causes were most closely associated with Hodgkin lymphoma and gonadal germ cell tumors, both highly treatable with current chemotherapeutic agents. In both of these cancers, as well as with osteosarcoma, the cause of death is often a secondary cancer that may be treatment-related [44].

Complications

With rapid advances in therapy, many more pediatric patients may survive into adulthood. Long-term sequelae of some treatments used in children are still being discovered. It is known that some patients have secondary treatment-related cancers, as well as long-term cardiac effects [44]. It is also important to note that pediatric cancer survivors have a higher than typical risk of suicide. This typically occurs in the third or fourth decade of life, indicating a need for long-term psychosocial support, and not just during active treatment [44]. It is important for emergency physicians to be aware of this and consider previous cancer as a risk factor when screening children and adults in the ED.

Common Pitfalls

New Onset

The most common pitfall of diagnosis is not considering an oncologic process in the differential of a vague complaint. A missed diagnosis can delay care or in severe cases be fatal. Additionally it is important avoid steroids in patients who present with new-onset wheezing without considering the possibility of a mediastinal mass.

Undergoing Therapy

The most common pitfall in patients receiving treatment is not recognizing the severe impact chemotherapeutic agents have on typical symptom presentations. The immunosuppressive therapies may also suppress typical systemic symptoms of disease.

Prevention/Upstream Drivers

Unlike many adult oncologic processes, there are very few pediatric cancers with specific, preventable causes. There is a significant increase in cancer among pediatric patients receiving organ transplants, primarily due to Epstein-Barr virus infection in conjunction with immunosuppression to prevent rejection [45]. Socioeconomics has not been linked to leukemic processes [46]. While some studies speculate that children born via artificial reproductive technologies have a higher risk of cancer, some recent studies refute this claim [47, 48]. Birth defects are associated with increased cancer risk, with some defects related to specific cancers [49]. Overall, genetic predisposition is believed to be the more common cause of disease than specific environmental exposures [50]. Prevention and recognition of secondary treatment-related complications should be enhanced with close monitoring by the patient's oncologist.

Future Needs/Vision

Pediatric oncologic is a rapidly changing field of medicine. Within the past 20 years, survival rates continue to improve. The rise of monoclonal antibody use in adults may soon be employed in pediatrics as well, with studies already being conducted with neuroblastoma [2, 3]. Emergency physicians should be aware that the complications of these medications in children are not well known; however, they may be similar to those in adults. Current studies suggest that the same weight-based dosing results in lower plasma levels in infants and children, which must be taken into consideration for future management [51].

Health Services/Resource Utilization

Studies show that, even with the same malignancy, pediatric patients, and specifically adolescent patients, have higher costs associated with treatment compared to adults. These increased costs are likely related to increased rates of hospitalization [52].

Policy/Legislative

Medicolegal

The most important component of ED management of patients with known oncologic processes is rapid evaluation. In these patients, as with every neutropenic fever patient, time is essential for infection control and hemorrhage management [15]. When available, notification prior to arrival with pre-ordering treatment for specific diagnoses, such as neutropenic fever, may improve time to administration of live-saving antibiotics.

Documentation/Quality Indicators

The main quality indicators in pediatric oncologic are focused on time to antibiotics in the setting of neutropenic fever. It is important to document the initial examination in detail as it may change rapidly, as well as repeat examinations that give a clear picture of any changes that occur.

Key Points/Pearls

Pattern recognition is key in pediatric cancer diagnosis. Staying vigilant is vital to avoid missing key diagnoses. Weight loss in children, unexplained bruising or bleeding, persistent and unexplained pain in back or extremities, new-onset wheezing, and mental status changes are particularly pertinent to cancer diagnoses.

The emergency provider should maintain a low threshold for detailed evaluation of the oncologic patient undergoing active therapy.

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Hyperleukocytosis and Leukostasis

36

Sharleen Yuan, Samantha J. Yarmis, and Kami M. Hu

Case Study

A 78-year-old male with a history of hypertension, coronary artery disease, and acute myelogenous leukemia is brought in by family for altered mental status. His family members state that he has not acted like himself for the last few days and has had a steady functional decline for the last few weeks to months. Additionally, he has experienced worsening shortness of breath with a fever of 101.2 degrees Fahrenheit (°F) that developed "the other day." The patient is alert but only oriented to self, which is inconsistent with his baseline. He has had no known sick contacts and is up to date on his immunizations. The patient denies any chest pain, upper respiratory symptoms, nausea, vomiting, diarrhea, numbness, tingling, or weakness. He has no history of alcohol or drug use. The rest of his history is unremarkable.

Physical Exam

Vitals: Temp 100.8 °F, BP 150/75 mmHg, HR 98 bpm, RR 32/min, O_2 saturation 89% on room air. General: Patient alert, but not oriented to place or time. Appears tachypneic when speaking but is in no acute distress. HEENT: Normal sclera, intact extraocular movements, pupils equal and reactive to light. Petechiae noted on buccal mucosa intraorally. Tympanic membranes are normal. Trachea midline. Cardiovascular: Regular rate and rhythm, with good S1 and S2. No murmurs, rubs, or gallops. Pulses 2+ bilaterally. Pulmonary: Rales bilaterally with faint expiratory wheezes throughout. Abdomen: Normoactive bowel sounds. Nontender, non-distended, with the spleen tip palpable 3 cm below the costal margin. Neuro: Cranial nerves intact to testing. Motor strength and sensation intact. Negative Romberg, normal gait. Skin: Scattered petechiae over bilateral upper and lower extremities. Extremities: Warm, well-perfused, without edema.

Laboratory Values

White blood cell count, 125 × 10^3/μ[micro]L (89% blasts); hemoglobin, 6.6 g/dL; hematocrit, 19.9%; platelets, 9 × 10^3/μ[micro]L; sodium, 137 mmol/L; potassium, 5.3 mmol/L; chloride, 104 mmol/L; bicarbonate, 22 mmol/L; blood urea nitrogen, 25 mg/dL; creatinine, 2.4 μ[micro]mol/L; calcium, 9 mg/dL; magnesium, 2.9 mg/dL; phosphorus, 4 mg/dL; troponin, <0.04 ng/mL; uric acid, 5.5 mg/dL; lactate dehydrogenase, 432 IU/L.

Imaging

Chest radiograph: Bilateral interstitial infiltrates without cardiomegaly, masses or effusions.

Management

The patient was determined to have hyperleukocytosis causing cerebral leukostasis. He received isotonic intravenous (IV) fluids in the emergency department (ED) and was transfused 1 unit of packed red blood cells and 1 pack of platelets. The on-call oncologist was consulted and hydroxyurea was started with a plan for leukapheresis given his altered mental status and worsening WBC count. He was admitted to the cancer service to further monitor his symptoms and was also treated with allopurinol for mild tumor lysis syndrome. By early the next morning, the patient had demonstrated a

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mild decrease in WBC count with the hydroxyurea alone, and there were extensive conversations with the patient's family regarding placement of a leukopheresis catheter and overall goals of care. In the end, the family decided on palliative measures and the patient was transitioned to inpatient hospice care.

Introduction

The leukemias are a broad group of hematologic malignancies encompassing acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia/lymphoma (ALL), and chronic lymphocytic leukemia (CLL) [1]. Given the prevalence of these malignancies, it is highly likely that the average emergency physician will encounter a patient at their first presentation for medical care. This chapter will discuss the ED management of hyperleukocytosis and resulting leukostasis, providing insights into necessary diagnostics and crucial steps for treatment. Other complications of leukemia are discussed elsewhere in the text.

Hyperleukocytosis is most often defined as a white blood cell (WBC) count of greater than 50,000 or 100,000 cells/microliter, but complications can occur at lower numbers, and absolute WBC count does not correlate directly with symptoms [2]. Although coined specifically to refer to the acute phase of CML, the term "blast crisis" is sometimes used to describe any hyperleukocytosis with predominant blasts. Hyperleukocytosis causes symptoms when the high concentration of circulating cells leads to leukostasis and impaired microvascular circulation causing organ damage, most commonly affecting the lungs and brain. Additional complications of hyperleukocytosis include tumor lysis syndrome (TLS) and disseminated intravascular coagulation (DIC), both independently life-threatening entities. Early recognition and treatment of this disease process is crucial to minimize the morbidity and mortality of these patients and to optimize them for attempts to cure of malignancy.

Epidemiology

Globally, leukemias are the eighth most commonly diagnosed cancer with 600,000 new cases annually and the ninth most common cause of cancer mortality with 353,000 deaths each year [3]. Of these, AML and CLL have the highest annual incidence rates with 190,000 and 191,000 new cases, respectively, while ALL carries the highest yearly mortality with approximately 110,000 deaths annually [3]. The overall incidence of leukemias has increased by 26% from 2005 to 2015, largely due to an aging global population as well as overall population growth [3]. With respect to pediatric patients, leukemias are the most common childhood cancer and the leading cause of both childhood and young adult (age 15–29 years) cancer deaths worldwide [3].

In the United States, leukemias are the 11th most commonly diagnosed cancer [3] with a 1.5% lifetime risk of developing any type of leukemia [4] and the sixth most common cause of cancer deaths each year. While there is a relatively even distribution between acute and chronic leukemia diagnoses annually, when divided by type, CLL is the most commonly diagnosed leukemia, followed by AML, CML, and ALL. The overall number of annual deaths from acute leukemia is two-thirds higher than those from chronic leukemias [5, 6] with AML responsible for the most deaths, followed by CLL, ALL, and CML [3].

Rates of leukemia vary by age and by ethnicity. Overall, acute leukemias are more common in non-Hispanic whites than in other ethnicities [7]. In terms of age, AML demonstrates a bimodal distribution, with a peak in infancy followed by a second peak beginning in young adulthood, with a median age at diagnosis of 69 years [8]. ALL also has a bimodal distribution with a slightly later peak in childhood and then a smaller second peak after the age of 60 [7], with a median age at diagnosis of 15 years. The median age at diagnosis is 65 years for CML and 70 years for CLL [8].

Overall survival for all forms of leukemia has improved, from 33% in 1975 to 59% in 2005 [4], but these gains in survival have been unevenly distributed with the greatest gains for patients with ALL, patients in younger age groups, and patients who are white. For the acute leukemias, the poorest survival is in those under 1 year of age, after which point the likelihood of survival is highest in older children and young adults and subsequently decreases with age [7]. Survival also varies widely by location; childhood ALL, for example, carries an overall survival rate ranging from 15% to 90% depending on the country, reflecting disparities in access to care [3]. As survival from childhood leukemias has improved, treatment-related mortality has accounted for an increased number of deaths, especially from ALL [9]. There are over 450,000 leukemia survivors in the United States [8], with several factors contributing to the increased survival over time. These factors include more intensive and standardized protocols for pediatric patients, the development of tyrosine kinase inhibitors (TKIs) and stem cell transplantation, and improved techniques for diagnosis and residual monitoring, including flow cytometry, polymerase chain reaction (PCR), and fluorescence in situ hybridization (FISH) testing [1, 4, 6].

Epidemiologic data on frequencies of ED presentations by patients with leukemia are scarce. A 2017 analysis of the Nationwide Emergency Department Sample found that of

the 29.5 million ED visits by patients with a cancer diagnosis over a 7-year period, 3.1% of those were by patients with a diagnosis of leukemia [10]. The existing published data on general ED usage indicates that solid tumors make up a larger contingency of ED visits [10, 11], but a case series from MD Anderson Cancer Center found that patients with leukemia accounted for the second highest percentage of annual visits by cancer patients (12.7%) with the highest admission rate for a specific cancer (83%) [12].

The incidences of hyperleukocytosis and leukostasis are dependent on the type of leukemia, and the presence or absence of certain genetic mutations affects an individual's risk. Perhaps because myeloid cells are larger than lymphoid cells, leukostasis occurs most often in AML and CML and can occur at lower white blood cell counts in the lymphocytic leukemias [13]. The incidence of hyperleukocytosis in adult patients with AML ranges from 5% to 13%, while it ranges from 10% to 30% for patients with ALL. While hyperleukocytosis is common in CLL, leukostasis itself is rare [14]. Hyperleukocytosis is similarly common in CML, but with more frequent clinical leukostasis occurring most often during blast crisis. Hyperleukocytosis is associated with markedly higher early mortality (approximately 20% in the first week) and modestly reduced 5-year overall survival for those who survive the initial phase [2].

Health Economics

The cost of general cancer care is rising rapidly [12, 15], and the management of leukemia is no exception. There are multiple drivers of healthcare expenditures in treating leukemia, including the cost of medications, the costs associated with the provision of both clinic and in-hospital care, and the costs related to the management of both expected and unexpected treatment-related complications [15, 16]. Treatment strategies for leukemia have expanded to include targeted oral chemotherapies and immunotherapies which often carry decreased treatment-related morbidity and mortality and the potential for increased longevity. These medications are often much more expensive than traditional chemotherapy, however, and are a significant driver of the increased costs of modern leukemia management, as exemplified by the 300% increase in per-patient lifetime cost of CLL treatment since the development of newer oral targeted therapies [15].

Treatment costs vary by leukemia subtype and type of treatment. Costs to the healthcare system range from approximately $88,000 per chronic leukemia patient to more than $450,000 per acute leukemia patient over the first year after diagnosis, with highly variable costs to patients themselves [17]. The need for inpatient care is a major driver, accounting for 55–70% of costs in the United States, depending on leukemia type [17–19], and hospitalizations for leukemia cost more per stay than any other type of cancer [20]. Direct cancer treatment, specifically anticancer drugs and hematopoietic stem cell transplantation (HSCT), accounts for a large portion of healthcare costs [17, 19].

For patients with incurable malignancy or poor prognosis, severe comorbid illness, and poor functional status or who have goals of care that focus on comfort rather than aggressive measures, palliative care consultation is associated with lower rates of intensive care unit (ICU) admission and lower healthcare costs, although such consultations rarely occur early [12, 21, 22].

ED visits are common among leukemia patients; in one study, 81% of patients with acute leukemias had at least one unplanned ED visit and/or hospitalization within the first year [23]. Common reasons for ED visits include fever, bleeding, gastrointestinal complaints, and respiratory symptoms [18]. Robust data on the cost of these unplanned visits as a portion of total leukemia healthcare expenditures is lacking.

Pathophysiology of Leukemia and Leukostasis

Both acute and chronic leukemias arise from abnormalities in hematopoiesis that lead to the proliferation of abnormal cells. The pathophysiology of each will be briefly discussed with the acknowledgement that the processes are complex and not yet fully understood. The increased availability of molecular techniques has led to recognition of greater heterogeneity among the leukemia subtypes than was previously known, and different subtypes of each disease may have different causal mechanisms [18].

In normal hematopoiesis, pluripotent hematopoietic stem cells in the bone marrow give rise to all hematologic cells, with various biochemical factors influencing their differentiation into common lymphoid or common myeloid progenitor cells [24]. Common lymphoid precursors mature within the lymphoid organs to become natural killer cells, T lymphocytes, and B lymphocytes [25], while common myeloid progenitor cells eventually give rise to basophils, neutrophils, eosinophils, macrophage, platelets, and erythrocytes [24]. Blast cells are the early manifestations of both lymphoid and myeloid cells. In healthy individuals, they comprise less than 5% of the cells in the bone marrow and should not be found in the peripheral blood.

In CML, there is abnormal proliferation of the myeloid lineage. The initial chronic phase, characterized by the accumulation of myeloid progenitors and mature myeloid cells in the blood and extramedullary tissues, is followed after 3 to 4 years by arrest of myeloid cell maturation and a transition to blast crisis [26]. Blast crisis is technically defined as the presence of greater than 20% blasts in the blood or bone

marrow with demonstration of extramedullary blast accumulation [1, 27, 28]. In over 90% of cases, patients have a characteristic acquired genetic abnormality, the Philadelphia chromosome, which is the result of translocation between the long arms of chromosomes 9 and 22 [t(9;22)], resulting in the creation of the BCR-ABL fusion gene [26].

AML, as its name suggests, does not have the initial indolent phase seen in CML. It is characterized by uncontrolled clonal expansion of myeloid progenitor cells, i.e., blasts. The accumulation of blasts interferes with the production of normal blood cells of all lineages – red blood cells, platelets, and normal white blood cells – leading to the common signs and symptoms of fatigue, easy bleeding and bruising, and fever and infection, secondary to anemia, thrombocytopenia, and neutropenia, respectively [16, 29]. Acute promyelocytic leukemia (APL, APML), an important subtype of AML with its own prognosis, complications, and specific treatment considerations, accounts for 5–10% of cases and is characterized by the translocation t(15;17) [30]. Several other mutations and cytogenetic abnormalities play key roles in recent targeted therapies [31].

A related malignancy, myelodysplastic syndrome (MDS), is characterized by cytopenias resulting from abnormal, ineffective bone marrow [24, 32]. An enormous variety of genetic mutations have been implicated in the development of MDS, with varying effects on prognosis [32]. Some subtypes of MDS are associated with excess, but fewer than 20%, blasts. The presence of greater than 20% blasts defines AML, and, in fact, having MDS dramatically increases the risk of developing AML [1, 33].

ALL occurs due to the clonal expansion of lymphoid progenitor cells which proliferate and accumulate in the bone marrow and other tissues [34]. Different subtypes are characterized by the type of lymphocytes involved, i.e., B or T cells, as well as the specific causative cytogenetic abnormalities, which have important prognostic and therapeutic implications. A complex interplay between multiple genetic mutations and environmental factors ultimately results in the development of ALL [35].

CLL is characterized by the accumulation of mature-appearing B lymphocytes in the blood, bone marrow, or other lymphoid tissues [36]. As in ALL, multiple incompletely understood genetic mutations and other factors result in CLL and determine severity and prognosis [37].

As already mentioned, hyperleukocytosis can cause a hyperviscous state and decreased tissue perfusion, although the fact that particularly high WBC counts may not always cause symptoms is still not fully explained. Theories regarding specific pathophysiology include the consideration that progenitor cells (blasts) are generally larger and less flexible than mature cells, making them more likely to block microvasculature. It has also been proposed that the rapid division of malignant cells, potentially in combination with the body's response to microvascular ischemia, releases specific cytokines and chemoattractants that further attract blast cells and activate the coagulation cascade, worsening the overall prothrombotic milieu [13]. The ongoing cell turnover of such a high volume of cells often leads to a pre-chemotherapy "spontaneous" tumor lysis syndrome. This turnover is also thought to increase the circulating concentration of tissue factor, a procoagulant, with ongoing endothelial damage and hypoxic events predisposing to the development of disseminated intravascular coagulation [2, 13].

Presentation

Leukostasis can be difficult to recognize, as its clinical manifestations mimic other common conditions such as infection, intoxication, acute cerebrovascular accident, and myocardial infarction [2]. The most common presenting symptoms are those of respiratory or neurologic involvement. Patients with pulmonary complaints may present with symptoms ranging from mild dyspnea on exertion to respiratory distress and hypoxia requiring mechanical ventilation. The pulmonary exam, similarly, may range from relatively normal to demonstrating focal findings or widespread abnormalities. Neurologic symptoms can range from focal neurologic deficits to generalized confusion or weakness, blurred vision, or decreased alertness, and a fundoscopic examination may reveal retinal hemorrhages or papilledema. Despite an elevated white count, patients with hyperleukocytosis actually have a functional neutropenia due to decrease in the amount of normal white blood cells, and up to 80% of patients with leukostasis develop fevers, most likely due to increased inflammation as well as high risk of concurrent infection given the patient's immunosuppressed state [28]. The electrolyte abnormalities associated with TLS may cause patients to present with arrhythmia, palpitations, or [pre]syncope, although these are not classic presentations of hyperleukocytosis. Leukostasis can affect any part of the body; the emergency physician should be wary of other organ system dysfunction such as renal insufficiency or myocardial ischemia and perform a thorough physical exam and appropriate diagnostics once hyperleukocytosis is identified [38]. Some common manifestations of leukostasis are listed in Fig. 36.1.

ED Evaluation

Because of the nonspecific nature of these patients' presenting symptoms, the diagnosis of leukemia and leukostasis are often not considered until bloodwork returns with an elevated WBC count, but once hyperleukocytosis is recognized, it is important to revisit the patient's presentation. Ensuring a thorough history is key, utilizing collateral from chart review

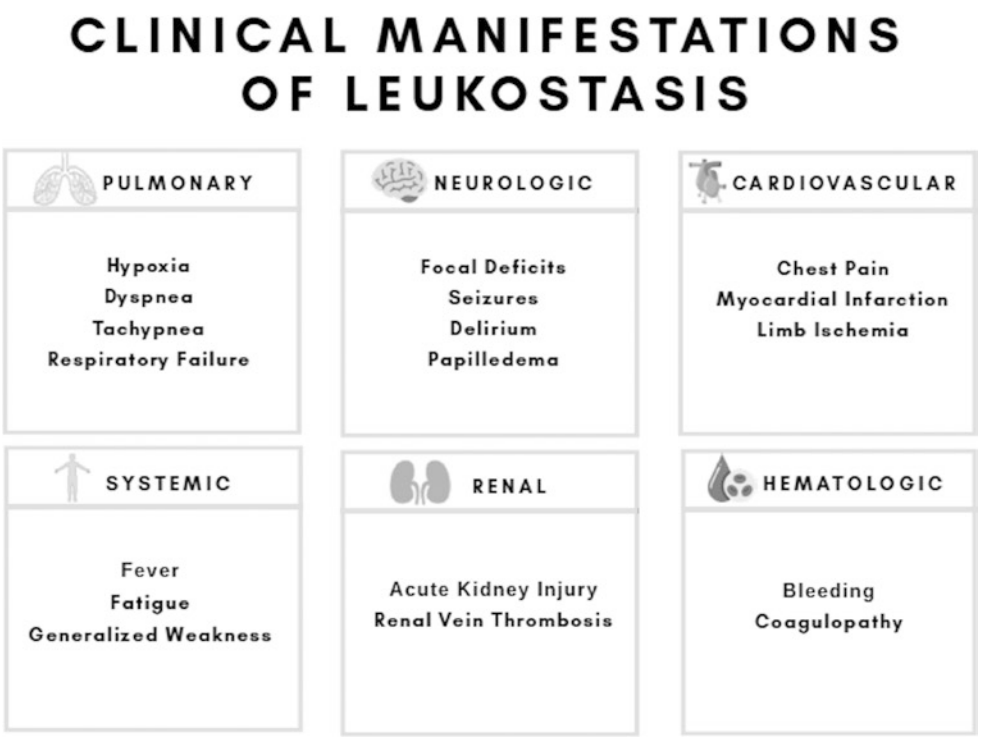

Fig. 36.1 Common manifestations of leukostasis

and available family or friends if the patient is unable to provide it. It may also be necessary to reexamine the patient to ensure all signs of potential organ dysfunction have been identified.

The gold standard diagnostic test for leukostasis is tissue biopsy demonstrating leukocyte-clogged blood vessels [39]. but this test is rarely performed. The diagnosis is now most often made based on a combination of clinical findings and diagnostics indicative of organ dysfunction in the setting of hyperleukocytosis. Laboratory testing in the ED should include a complete blood count (CBC) with differential, peripheral blood smear, complete metabolic panel (CMP) including magnesium and phosphorus levels, prothrombin time with international normalized ratio (PT/INR), partial thromboplastin time (PTT), fibrinogen, D-dimer, fibrin-split products, uric acid, lactate dehydrogenase (LDH), and type and screen. A troponin should be collected in patients with chest discomfort or other concern for myocardial ischemia, and a blood gas obtained for pH determination in patients with metabolic acidosis and acute renal failure. A venous blood gas (VBG) is usually the most appropriate as arterial blood gas (ABG) oxygenation values are inaccurate due to ongoing oxygen consumption by the many leukocytes in the blood collection tube [28]. This "pseudohypoxemia" can be partially mitigated by sending the ABG to the lab on ice. Blood cultures should be obtained in febrile patients, with urine culture added if urinalysis is consistent with infection and sputum culture if patient has a productive cough. An electrocardiogram should be obtained to evaluate for signs of leukostasis-induced ischemia or other pathology secondary to metabolic abnormalities.

Imaging should target the symptoms exhibited by the patient. In patients with respiratory complaints, a chest x-ray should be obtained, and if clear, a non-contrast computed tomography (CT) scan of the chest should be pursued. Chest imaging may demonstrate a wide range of abnormalities, including interstitial edema, consolidation, focal or diffuse airspace opacities, and effusion or other infiltrates [40]. While malignancy is generally associated with an increased risk of venous thromboembolism, patients presenting with new leukemia and hyperleukocytosis prior to treatment are much more likely to have pulmonary leukostasis (reported incidence of 30–34% in AML) [41, 42] than pulmonary embolism (PE) (reported incidence of 3.4% to 5% for all leukemias) [43]. Indiscriminate evaluation by contrasted CT angiography should therefore be avoided if possible, given the high risk of renal dysfunction in this population. Although specific leukemias, such as CML and APL, carry higher risks for the development of venous thromboemboli (VTE), they are most often treatment-related, whether associated with the presence of a central venous catheter or the chemotherapy used [43, 44]. In cases of legitimately high concern for PE, CT must be pursued as ventilation-perfusion (VQ) scans have limited ability to discriminate between VQ mismatch caused by leukostasis versus embolism [45]. A non-contrast CT of

the head should be included if there are neurologic symptoms, and it may demonstrate ischemia, hemorrhage, or intracranial mass [46–48]. Depending on the neurologic deficits present, a nondiagnostic CT may indicate a need for further evaluation with magnetic resonance imaging (MRI). The presence of abdominal tenderness on exam may warrant imaging of the abdomen, whether by ultrasound or CT.

ED Management

The mainstay of ED leukostasis management is supportive therapy adhering to the ABCs – or CABs – of emergency medical care, as well as management of concomitant TLS or DIC, if present. While the basics of TLS and DIC treatment will be touched upon here, more thorough discussion can be found elsewhere in the text, and a summary of treatments can be found in Fig. 36.2.

Circulation

Hypotension is not classically seen in this patient population unless they also have severe metabolic acidosis or shock due to another etiology, but isotonic crystalloid IV fluids are a key component of leukostasis treatment for the purpose of hemodilution to decrease blood viscosity. Intravenous fluid administration also helps manage concomitant TLS and preserve kidney function. In patients without a reduced ejection fraction, it is recommended that IV fluids be given to a target urine output of 2 ml/kg/hr [49]. The use of furosemide may be considered if urine output falls below 100 ml/hr, in order to allow continued IV fluid administration, but should be used with caution as diuretics can worsen hyperviscosity and are relatively contraindicated in hypotension unrelated to cardiac volume overload. If the blood pressure is not adequately supported with hydration, a vasopressor such as norepinephrine should be used to maintain a mean arterial pressure (MAP) of greater than 65 mmHg. In patients with decompensated heart failure, use of an inotrope such as epinephrine is more appropriate, keeping in mind that at higher doses (above 0.05 mcg/kg/min) there is more alpha-1-receptor effect and pulmonary vasoconstriction may ensue, worsening potential cardiopulmonary instability.

There should be high suspicion for DIC in patients experiencing hemorrhage, whether pulmonary, intracranial, or another source. If the patient is not bleeding or is hemodynamically stable with small volume blood loss, aggressive packed red blood cell transfusion is not recommended due to its likelihood of worsening hyperviscosity. In patients without hemorrhage, early platelet transfusions should be performed to maintain platelet counts greater than 20,000 µ[micro]L to avoid spontaneous bleeding [50]. If the patient has CNS or intraocular hemorrhage, the platelet goal should be greater than 100,000 µ[micro]L, with a goal of 50,000 µ[micro]L for bleeding at other sites. Patients with DIC and fibrinogen levels less than 150 mg/dL should receive cryoprecipitate transfusion [51].

Patients with acute renal failure, whether secondary to renal ischemia from leukostasis, the renotoxic effects of lysed cell contents, or a combination of both, may exhibit a severe metabolic acidosis depending on the severity of renal injury, with secondary vasodilation and hypotension [52]. Consultation to the nephrology team may be indicated for emergent renal replacement therapy if there is not marked improvement with IV fluids, but the patient with hemody-

Emergency Department Leukostasis Mangement

Leukostasis	Intravenous Fluids	Hydroxyurea	Leukapheresis
Tumor lysis	Intravenous fluids	Address electrolyte abnormalities	Allopurinol +/– Rasburicase
DIC	Cryoprecipitate	Platelets (If below goal)	Red blood cells*

Fig. 36.2 Summary of ED treatments for leukostasis management. DIC = diffuse intravascular coagulation. *Red blood cell transfusion for hemorrhagic shock only, until white blood cell count decreased

namic instability and metabolic acidosis with a pH less than 7.2 should be temporized with IV sodium bicarbonate infusion [53] in addition to support with vasopressors if needed.

Airway/Breathing

The most acutely pressing issue for patients with leukostasis can be mild hypoxia or respiratory failure, both of which should be managed with the appropriate respiratory support from simple nasal cannula up to and including intubation if necessary. Patients may also present with increased work of breathing without pulmonary leukostasis secondary to respiratory compensation for metabolic acidosis. Strong consideration should be given to intubation in these patients, in order to decrease their metabolic workload and prevent decompensation when their respiratory muscles fatigue. It is crucial to remember to match their minute ventilation while still paralyzed post-intubation to avoid loss of their compensatory alkalosis and subsequent hemodynamic decompensation.

Other Treatment Considerations

Patients with leukostasis and TLS, characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia with or without acute kidney injury, should receive allopurinol, dosed appropriately according to renal function, in addition to IV fluids. If uric acid levels are high, typically greater than 8 mg/dL, a single dose of rasburicase, an effective uric acid-lowering agent [54], may be given in the ED. The electrolyte derangements should be managed as usual, with severe hyperkalemia sometimes requiring emergent dialysis if unresponsive to standard measures. The hypocalcemia that may be seen in parallel to hyperphosphatemia is due to phosphate binding with calcium and, as such, should not be repleted unless the patient is symptomatic or the hyperphosphatemia has been corrected, as IV calcium may cause intravascular calcium-phosphate crystal precipitation and renal failure.

Emergency physicians should maintain a low threshold to obtain cultures and administer empiric antibiotics in patients with hyperleukocytosis and fever, as they are functionally neutropenic [28]. Although these patients are in a hypercoagulable state, without a clear diagnosis of life-threatening venous thromboembolism, prophylactic antiplatelet and anticoagulant medications should not be given due to the patient's high risk of bleeding. It is recommended that patients with identified TLS or DIC or who are unstable should have a CBC, BMP with magnesium and phosphorus, uric acid and coagulation panel, including fibrinogen, with consideration given to pH monitoring as well, measured every 4 to 6 hours while in the ED [55].

Definitive Treatment

The definitive management of hyperleukocytosis and leukostasis is leukocytoreduction, which can be achieved by three methods: administration of hydroxyurea, leukapheresis, and initiation of appropriate chemotherapy. Emergent consultation with the oncologist is crucial to determine the plan for cytoreduction. While hydroxyurea is generally widely available and effective and in most instances should be started immediately, it can take 24 to 48 hours to demonstrate its cytoreductive effect. On the other hand, leukapheresis is rapidly effective but in most cases requires central venous access and is not performed at all centers, potentially requiring transfer to another facility. If the patient is symptomatic, emergent leukapheresis for leukocytoreduction is the treatment of choice, although there is no consistent data to indicate that it improves overall mortality [13]. The emergency physician should note that if placement of a central line is required during their care of the patient, it is helpful to avoid the right internal jugular in case leukapheresis or emergent hemodialysis is indicated, as it is the preferred site for apheresis/dialysis catheter placement.

Disposition and Prognosis

Leukostasis is a medical emergency. Without immediate recognition and treatment, a patient presenting with new onset leukemia and leukostasis with both pulmonary and neurologic symptoms has a 1-week mortality rate of 90% [56]. Pulmonary involvement is an independent predictor of hospital mortality and has been identified as the single worst prognosticator for overall morbidity and mortality [41]. Although other predictors of in-hospital death include altered mental status and non-white race [12], overall mortality of individuals with leukostasis is 40%. A diagnosis of leukostasis requires admission to an inpatient team; the level of care is determined by the patient's clinical stability and hospital resources and protocols.

In consultation with the oncologist, the management of stable, asymptomatic patients sent to the ED for lab abnormalities who exhibit hyperleukocytosis without leukostasis is often less "exciting." These patients can be started on hydroxyurea and IV fluids without much fanfare, depending on the level of hyperleukocytosis, and admitted to the inpatient service. Stable tumor lysis syndrome without life-threatening electrolyte derangements or metabolic acidosis can similarly be started on allopurinol and/or rasburicase

with IV hydration and appropriate lab monitoring. The presence of DIC, even without hemorrhage, warrants closer monitoring as serious bleeding can develop quickly.

For patients with severe medical comorbidities or poor baseline functional status, initiation of palliative services in the ED may be warranted. An increasing number of cancer patients die in the hospital, and leukemia has the second highest in-hospital mortality rate at 16%. Early initiation of palliative care, especially in the ED, has been associated with improved patient symptom management, decreased utilization of hospital resources, and decreased hospital costs [12, 21, 22, 57, 58].

Future Research

Most of the research regarding economic impact and ED utilization is small-scale and limited with respect to the leukemias specifically. Further research into cost and number of and reasons for ED visits, with and without subsequent hospitalization, would be helpful in defining the scope of the problem, assessing changes over time and investigating interventions to decrease healthcare costs and ED utilization.

Only 2–4% of palliative care consults for cancer patients take place in the ED, and consultation often occurs close to the time of death [12]. Research into factors leading to late palliative consultation and factors influencing ED referrals could have a significant impact on the quality of life of leukemia patients, as well as avoiding unnecessary and/or unwanted hospitalizations in these patients. The development of predictive models to determine hospital mortality for patients with leukemia, which could be applied in the ED, could be useful for both patients and physicians.

Several subgroups of patients have been underrepresented in large clinical trials, which may contribute to disparities in care. These include racial minorities and elderly patients [8, 15, 18]. As patient populations continue to increase in age and medical complexity over time, more specific research into both curative and palliative treatments for these sicker patients is needed.

Conclusion

The collective leukemias are some of the most common malignancies worldwide, resulting in more than half a million new cases yearly. Leukostasis is a medical emergency that must be promptly recognized by the emergency physician and is commonly accompanied by other potentially life-threatening disease processes such as tumor lysis syndrome and disseminated intravascular coagulation. Leukostasis presents nonspecifically and may mimic other disorders. High clinical suspicion is warranted if the patient has a history of hematologic malignancy, and the diagnosis should be quickly identified once hyperleukocytosis is detected. Patients with leukostasis not only require supportive care but also directed therapies to improve outcomes, making it crucial for emergency clinicians to not only be aware of this process but to also know how to take the appropriate steps to manage it.

Pearls

- Leukostasis refers to the clinical effects of blood hyperviscosity and impaired tissue perfusion secondary to hyperleukocytosis and can present with a broad range of symptoms, most often respiratory or neurologic.
- The mainstays of leukostasis management include hemodilution with IV fluids, supportive therapy including respiratory and hemodynamic support if needed, leukocytoreduction with hydroxyurea +/− leukapheresis, and ultimately chemotherapy.
- Pulse oximetry is more accurate than ABGs for assessment of oxygenation, as there is continued oxygen consumption by the leukocytes in the ABG syringe.
- Patients with hyperleukocytosis should be screened for TLS and DIC, which increase mortality and should be quickly addressed. If the patient is unstable and remains in the ED for an extended period, labs should be obtained every 4 to 6 hours.
- Packed red blood cell transfusion should be avoided in relatively stable patients as it worsens viscosity and can further impair perfusion.
- Hydroxyurea is indicated even for asymptomatic or mild symptoms, starting at 50–100 mg/kg/day until WBC decreases appropriately.

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Bleeding and Thrombosis

37

Thomas G. DeLoughery

Case Study

A 67-year-old man was receiving gemcitabine for metastatic pancreatic cancer. He has noticed after the fourth cycle of treatment his blood pressure was starting to rise. When he presented for his sixth cycle of therapy, his oncologist noted that his platelets were decreased to 50,000/uL. Review of the blood smear showed 2–3 schistocytes per high-power field. His creatinine had risen to 2.3 mg/dL and LDH was five times normal. A diagnosis of gemcitabine-induced thrombotic microangiopathy was made. Despite holding gemcitabine, his laboratory findings continued to worsen. Anti-complement therapy with eculizumab was started with a loading dose of 900 mg weekly and then 1200 mg every other week. Within 2 weeks, his platelets started to rise and his LDH fell. By 2 months, his creatinine had normalized. Given complete resolution of his thrombotic microangiopathy, his anti-complement therapy was stopped. At 1-year follow-up, he had no signs of recurrence of his thrombotic microangiopathy.

Introduction

Cancer patients can suffer both bleeding and thrombotic complications, which can impair both quality of life and survival. These complications can be due to the effects of the cancer itself or its therapy. This chapter will review these complications and offer guidance to diagnosis and treatment.

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Bleeding

Bleeding Related to Coagulation Factors

Acquired von Willebrand Disease Acquired von Willebrand disease (VWD) can complicate hematological malignancies – lymphomas, myeloproliferative neoplasms, myeloma, and monoclonal gammopathies [1]. Acquired VWD should be considered when a patient with these types of tumors presents with excess bleeding – especially nosebleeds or gastrointestinal bleeding [2]. Both type 1 (decreased total von Willebrand protein) and type 2 (loss of high molecular weight multimers) VWD can be seen.

Patients with acquired VWD have variable responses to therapy for acute bleeding [3]. Desmopressin is effective for patients with acquired VWD types 1 and 2, but the magnitude and duration of effect are often reduced. For bleeding or for surgical procedures, high doses of the von Willebrand concentrate Humate-P or recombinant von Willebrand factor are indicated with careful monitoring of levels. For patients with very strong inhibitors that factor concentrates cannot overcome or those with life-threatening bleeding, rVIIa may prove useful.

Acquired Factor VIII Inhibitors Factor VIII deficiency is the most frequent acquired coagulation factor deficiency seen in cancer patients [4]. There are also cases reported after use of checkpoint inhibitors [5, 6]. Patients will have prolonged aPTTs, a positive screening test for a factor inhibitor, and a low factor VIII level. For severe or life-threatening bleeding, recombinant VIIa is the treatment of choice [7]. The dose is 90 ug/kg repeated every 2–3 h until bleeding has stopped. The key step beside controlling bleeding is to eliminate the autoantibody with immunosuppression starting with prednisone 60 mg/day and adding oral cyclophosphamide 100 mg po plus rituximab either 375 mg/m^2 weekly × 4 or 1000 mg separated by 14 days. Eradication of the autoantibody does not require successful tumor treatment

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and should be attempted before major procedures such as tumor resection are planned.

Bleeding Related to Platelet Number and Function

Immune Thrombocytopenia Immune thrombocytopenic purpura (ITP) has been reported in 2–4% of patients with chronic lymphocytic leukemia, myeloma, and Hodgkin's disease [8]. ITP can occur during any part of the course of the tumor including when the patient has responded to antineoplastic therapy. The presentation of ITP in cancer patients is not different than in those with other conditions; patients present with petechia and other stigmata of bleeding. Why ITP occurs during the course of lymphoproliferative disease is not well understood, although a disturbed immune system could possibly predispose patients both to the lymphoproliferative disorder and to thrombocytopenia [9, 10]. Increasingly, ITP and other autoimmune cytopenias are being reported as complications of the use of checkpoint inhibitors [11]. Therapy for the ITP that complicates tumors/checkpoint therapy is the same as that for classic immune thrombocytopenia. High-dose corticosteroids such as pulse dexamethasone 40 mg/day × 4 days (plus immunoglobulin 1 gram/kg IV if necessary) are given first, but if an adequate platelet count cannot be maintained, then the choice is between splenectomy, thrombopoietin agonists, and rituximab.

Thrombotic Thrombocytopenic Purpura Thrombotic thrombocytopenic purpura (TTP) should be suspected when a patient presents thrombocytopenia, microangiopathic hemolytic anemia (schistocytes and signs of hemolysis), and any evidence of end-organ damage [12]. Diagnosis is confirmed by finding a low ADAMT13 level (<10%). TTP has a unique presentation in cancer patients with evidence of metastatic cancer in the bone marrow and lungs [13, 14]. These patients can have extensive intravascular tumor leading to thrombocytopenia and schistocytes. Plasma exchange is ineffective in these patients, but resolution of the TTP has been reported if the tumor is responsive to antineoplastic therapy.

Therapy-Related Thrombotic Microangiopathy Thrombotic microangiopathies (TM) can complicate a variety of therapies such as calcineurin inhibitors, proteasome inhibitors [15], and gemcitabine [16]. The most common antineoplastic drug causing TM is gemcitabine with an incidence of 0.1–1% [17, 18]. The appearance of the TM syndrome associated with gemcitabine can be delayed, and the condition often is fatal. Severe hypertension often precedes the clinical appearance of the TM. The use of plasma exchange is waning due to lack of effectiveness, and there are increasing reports of the successful use of the complement inhibitor eculizumab [19].

TMs can complicate stem cell marrow transplants [20, 21]. The incidence ranges from 15% for allogeneic to 5% for autologous bone marrow transplants. Several types of TMs are recognized in bone marrow transplantations. One is "multi-organ fulminant" which occurs early (20–60 days) with the evolution of multi-organ system involvement and is often fatal. Another type of TM is similar to calcineurin inhibitors TMs. This occurs within days after the agent is started with the appearance of a falling platelet count, falling hematocrit, and rising serum LDH level [22]. With withdrawing the agent, the TM resolves. A "conditioning" TM, which occurs 6 months or more after total body irradiation, is associated with primary renal involvement. Finally, patients with systemic CMV infections can present with a TM syndrome related to vascular infection with CMV. The etiology of bone marrow transplant-related TM appears to be different from that of "classic" TTP since alterations of ADAMTS13 have not been found in stem cell transplant-related TTP implicated therapy-related vascular damage. There is increasing evidence that disorders of complement regulation may be the etiology of early stem cell transplant TM. Although plasma exchange is often tried, response is poor for TTP/HUS. There are increasing reports of successful use of the complement inhibitor eculizumab, and this agent should be used, especially if there are signs of complement dysregulation such as high C5-9 levels [23, 24].

Specific Hematological Cancers Associated with Bleeding

Acute Promyelocytic Leukemia (APL)

Patients with APL have a higher risk of hemorrhagic death during induction therapy when compared with patients with other forms of leukemia [25]. The hemostatic defects in patients with APL are multiple with most having evidence of DIC at the time of diagnosis with bleeding still being the major cause of early death [26]. Life-threatening bleeding such as intracranial hemorrhage may occur at any time until the APL is put into remission. The etiology of the hemostatic defects in APL is complex and is thought to be the result of DIC, fibrinolysis, and the release of other procoagulant enzymes [25–27]. Therapy of APL involves treating both the leukemia and the coagulopathy (Table 37.1). Currently the standard treatment for APL is trans-retinoic acid (ATRA) in combination with chemotherapy or arsenic [28, 29]. This will induce remission in over 90% of patients, and a sizable majority of these patients will be cured of their APL. ATRA

Table 37.1 Acute promyelocytic leukemia

Consider diagnosis in any patient with leukemia presenting with coagulopathy
Start empiric all-trans-retinoic acid 45 mg/m^2/day in two divided doses while performing work-up
Coagulation goals
Fibrinogen greater than 150 mg/dL
Platelets greater than 50 × 10^9/L

therapy will also lead to the early correction of the coagulation defects, often within the first week of therapy. Given the marked beneficial effect of ATRA on the coagulopathy of APL and its low toxicity, it should be empirically started for any patient suspected of having APL, while specific testing is being performed. Therapy for the coagulation defects consists of aggressive transfusion to maintain the fibrinogen level at over 150 mg/dL and the platelet count at over 50 × 109/L.

Myeloproliferative Neoplasms

Bleeding can be seen in many of the myeloproliferative neoplasms, but rarely results in major morbidity [30, 31]. In patients with essential thrombocytosis, the risk of bleeding appears to increase with platelet counts above one million – perhaps due to the large amount of platelets absorbing von Willebrand factor. Most bleeding in myeloproliferative neoplasms consists of platelet-type bleeding – mucocutaneous bleeding or bruising with only a few reports of major bleeding. The use of drugs that inhibit platelet function such as aspirin is associated with a higher incidence of bleeding. Patients with extreme thrombocytosis and bleeding will respond to lowering the counts to below 1000 × 109/L [1]. Patients with myeloproliferative neoplasms should be screened for VWD before surgery or starting antiplatelet therapy. Rare patients with myeloproliferative neoplasms will have an acquired factor V deficiency with symptomatic patients presenting with bleeding and variable elevation of the INR and/or aPTT [32, 33].

Dysproteinemia

Multiple coagulation abnormalities have been described in patients with dysproteinemia, which can lead to severe bleeding [34, 35]:

- Abnormal clot retraction
- Abnormal fibrin clot
- Anti-glycoprotein IIb/IIIa antibodies
- Factor VIII inhibitor
- Heparin-like anticoagulation
- Impaired fibrin polymerization
- Inhibition of thrombin time

Therapy for the hemostatic defects in the dysproteinemic syndromes includes removal of the offending protein, either by reducing synthesis by treating the myeloma with aggressive chemotherapy or by plasmapheresis if the patient is having acute symptoms.

Patients with amyloidosis can have a marked increase in easy bruising and other bleeding symptoms which may be the first clue to diagnosis [36]. The most common defect is an elevation in the thrombin time which is seen in 30–80% of cases. A rare but important cause of bleeding in patients is systemic fibrinolysis. The patients may have decreased levels of alpha-2-antiplasmin and an abnormal euglobulin clot lysis time. The use of fibrinolytic inhibitors such as tranexamic acid has both corrected laboratory tests of fibrinolysis and reduced bleeding symptoms. Like with myeloma, treatment of the amyloid will correct the bleeding diathesis.

Coagulation Defect Due to Therapy

Bleeding has been reported with the use of tyrosine kinase inhibitors used in CML therapy, but it's unclear if this is due to the drug effect or the underlying disease. Many of these agents have been reported to lead to in vitro platelet dysfunction, but for most patients this does not appear to be clinically significant [37]. Bleeding has also been reported with inhibitors of VEGF [38]. Bevacizumab in particular is associated with bleeding – especially after surgery or with treatment of squamous cell carcinoma of the lung. In these cases, the bleeding may be more related to lack of wound healing and tumor necrosis. The BTK inhibitor ibrutinib is associated with a 5% incidence of bleeding including subdural hematoma, with the mechanism appearing to be via decreased platelet aggregation [39–41]. The new BTK inhibitor acalabrutinib – being more selective – may be associated with less bleeding [42].

Cancer and Thrombosis

Epidemiology

Thrombosis can be the presenting sign of cancer [43, 44]. As many as 10–20% of older patients who present with an idiopathic deep venous thrombosis will be found to have cancer on initial evaluation. Furthermore, over the next 2 years, up to 25% of these patients will develop cancer. Certain presentations of thrombosis are more worrisome for underlying cancer as a cause of the thrombosis: warfarin-refractory thrombosis, idiopathic bilateral deep vein thrombosis, or

both arterial and venous thrombosis. The cancers most frequently associated with thrombosis are adenocarcinoma of the lung and gastrointestinal cancers, especially pancreatic. Primary brain tumors are also associated with a higher risk of thrombosis as well as kidney, ovarian, and uterine cancers [43]. Thrombosis rates for breast and prostate cancer are not as extreme [45]. The co-existence of cancer and thrombosis has implications for both disease processes [46]. Cancer raises the risk of both anticoagulant-induced bleeding and breakthrough thrombosis, while the presence of a thrombosis worsens the cancer prognosis.

Given the data that thrombosis can be an early sign of cancer, one question that commonly arises is "Should a patient who presents with an idiopathic thrombosis be aggressively worked up for cancer?" Studies to date have not shown benefit of extensive evaluations of these patients for cancer, and current recommendations are age-appropriate cancer screening and complete work-up of any worrisome signs – such as guaiac-positive stools.

Increasingly common in cancer patients is the finding of an "incidental" pulmonary embolism on a CT obtained for tumor staging or evaluation of response to chemotherapy. Despite the "incidental" nature of finding the thrombosis, the prognosis is just as ominous as any cancer-related thrombosis, and these need to be aggressively treated with anticoagulation [47]. Also in cancer patients, distal vein thrombosis has a high recurrence rates and mandates long-term anticoagulation [48].

Rare patients can present with thrombosis and associated disseminated intravascular coagulation. These patients with tumor-related DIC have thrombosis in the setting of low platelets and decrease coagulation factors. These patients may also develop a non-bacterial thrombotic endocarditis and have multiple arterial embolic events.

The etiology of the cancer-related thrombosis is complex with many factors potentially playing a role [49, 50]. Tumors may directly activate factor VII by tumor-expressed tissue factor, as well as factor X. Patients with cancer have elevations of inflammatory cytokines that can further augment the hypercoagulable state. Treatment of the cancer can also lead to thrombosis. As discussed below, chemotherapy – especially cisplatinum, fluorouracil, and asparaginase – increases the risk of thrombosis. Biological agents such as thalidomide and lenalidomide also increase thrombosis risk. Surgery for cancer patients increases the risk of thrombosis threefold over similar operations in non-cancer patients [51].

Treatment

Cancer-related thrombosis requires aggressive anticoagulation [52, 53]. While in the past low molecular weight heparin (LMWH) was the treatment of choice, this has now shifted to the direct oral anticoagulants (DOAC). There are three large clinical trials of LMWH vs DOAC that show that DOACs are as effective, if not more effective, in the prevention of recurrent thrombosis with a slighter higher risk of bleeding [54–56]. This higher bleeding risk is only seen with upper gastrointestinal cancers and not with the use of apixaban. Two clinical trials have also shown the benefit of prophylactic dosing of DOAC by preventing the first cancer thrombosis in higher thrombotic risk patients [57, 58]. However, given the low absolute risk reduction in thrombosis, widespread use remains controversial.

Patients who have recurrent thrombosis while taking direct oral anticoagulants need to be treated indefinitely with LMWH. The rare patient who fails LMWH may benefit either from raising the dose by 25% or changing to fondaparinux [59].

Brain tumors or brain metastases are not a contraindication to anticoagulation. The only exceptions are brain metastases from thyroid cancer, melanoma, renal cancer, or choriocarcinoma, as these tumor metastases have a high rate of bleeding [60]. It should be remembered that placement of an inferior vena cava filter without concurrent anticoagulation is associated with an unacceptable rate of complications, including death from massive thrombosis.

Specific Situations

Myeloproliferative Neoplasms

Thrombosis is the most common cause of death in the myeloproliferative neoplasms [31, 61]. Correlation of thrombosis with blood counts depends on the underlying disease – patients with polycythemia rubra vera are at risk of thrombosis with hematocrits over 45%, but those with essential thrombocytosis can have thrombosis with platelets in the 4–600 × 109/L and as noted before may have greater risk of bleeding with counts greater than 1000 × 109/L. Patients with myeloproliferative neoplasms have a higher risk of thrombosis even with relatively normal blood counts, suggesting an intrinsic defect in the blood cell or vascular endothelium leading to thrombosis.

Patients with myeloproliferative neoplasms have a predilection for several types of thrombosis. Patients with Budd-Chiari and other visceral vein thromboses have a high incidence of underlying myeloproliferative syndromes [62]. Patients with essential thrombocytosis can also have platelet occlusion of the small digital vessels leading to erythromelalgia. These patients will have swollen, red, and very painful digits. The patients may only have slightly elevated platelet counts and are often misdiagnosed with arthritis. A diagnostic clue is that these patients will respond dramatically to a single aspirin per day.

Certain patients, especially those with Budd-Chiari syndrome, may have an "occult" myeloproliferative syndrome with maybe no evidence of any hematological disorder but have genetic evidence of myeloproliferative disease with

positive testing for the *JAK2* mutation. Interestingly, the *CALR* mutation – seen in 30–50% of patients with essential thrombocytosis – has not been associated with visceral vein thrombosis in patients with normal blood counts [63].

Heparin followed by warfarin or direct oral anticoagulants is indicated for most patients with acute venous thromboembolism complicating the myeloproliferative disorders. In a few instances, liver transplantation has been successful in treating liver failure due to Budd-Chiari syndrome – but these patients require long-term anticoagulation.

Antiplatelet therapy is recommended for treatment of patients with arterial thrombosis. Low doses of aspirin (81 mg/d) are preferable in patients with myeloproliferative neoplasms because the risk of bleeding with aspirin is dose related. There is increasing data that dosing 81 mg bid may be more effective [64, 65]. There is currently no data concerning the use of newer agents such as clopidogrel, but it may be reasonable for patients allergic to aspirin.

In addition to antithrombotic therapy, treating elevated blood counts is also important for patients with a history of thrombosis [66, 67]. For patients with thrombocytosis, hydroxyurea (1 gm daily to start) is the preferred therapy as trials have shown antithrombotic benefit. For younger patients who have concerns about hydroxyurea, weekly PEGylated interferon starting at 45–90 ug is another consideration. For patients with polycythemia, reduction of the hematocrit to under 45% with phlebotomy, hydroxyurea, or interferon is crucial [68]. There is increasing data for using the *JAK2* inhibitor ruxolitinib for blood count control in patients intolerant of other therapy, and this is another treatment option with retrospective data showing reduction in thrombosis [69, 70].

A common issue is whether to reduce platelet counts or to give aspirin to patients with thrombocytosis who do not have a history of thrombosis. Platelet reduction with hydroxyurea or interferon should be considered in asymptomatic patient if they are older (>65 years) or they have atherosclerosis, risk factors for arterial disease or symptoms of vascular ischemia. Some studies indicate that an elevated white count or the presence of the *JAK2* mutation may also be a risk factor for thrombosis [71]. All patients diagnosed with polycythemia should have their hematocrits reduced to less than 45% with either phlebotomy or cytoreduction [68]. Aspirin should be used in all patients with polycythemia (unless they have a bleeding diathesis). For patients with thrombocytosis, those at low risk of thrombosis do not benefit from aspirin [72].

Paroxysmal Nocturnal Hemoglobinuria (PNH)

One of the leading causes of morbidity and mortality in patients with PNH is thrombosis with patients presenting with either venous or arterial disease [73, 74]. PNH is also associated with a high incidence of visceral vein thrombosis. The cause of the hypercoagulable state is unknown, but complement-activated platelets have been implicated. In two large series pre-dating specific anti-compliment therapy, the rate of thrombosis in PNH was 28–39% with thrombosis leading to death in 58% [73, 75]. The development of the complement inhibitor eculizumab has led to control of the hemolysis in most patients with PNH, and there is strong evidence it also reduces thrombosis rates [76]. Eculizumab or ravulizumab [77] should be used in any patient with PNH who has had thrombosis, severe hemolysis, or a significant PNH clone (>50%). Although PNH is rare, patients with visceral vein thrombosis, thrombosis with unexplained high LDH levels, recurrent or warfarin-refractory thrombosis, or thrombosis in the setting of pancytopenia should be screened for PNH.

Venous Catheter Thrombosis

Central venous catheters are essential to many aspects of cancer therapy, but the clinically apparent thrombosis incidence for catheters is estimated to be 3–6% [78]. The signs of catheter thrombosis are non-specific, and the incidence of thrombosis is thought to be underestimated (Table 37.2).

Patients with catheter-related thrombosis often notice arm pain and swelling. Diagnosis of the thrombosis is made by Doppler, but some patients may only have central vein thrombosis and may require venography or CT angiography to make the diagnosis. Many patients have the diagnosis found while undergoing imaging for other reasons.

Therapy is not well defined. Data is increasing for peripherally inserted central catheters that simply removing the catheter may be the safest approach as the risk of bleeding with anticoagulation is high – reserving anticoagulation for the severely symptomatic [79]. For thrombosis with tunneled lines, anticoagulation should be given – unless the risk of bleeding is substantial. One trial does show that one can keep the catheter in place with 3 months of anticoagulation [80]. Prevention of catheter thrombosis is difficult as prophylaxis has not been shown to be a benefit.

Table 37.2 Options for catheter thrombosis

Peripheral inserted central catheters
Removal of catheter
Reserve anticoagulation for very symptomatic patients
Tunneled central catheters
Evaluated if line is needed
If removed, short-term anticoagulation if no bleeding risk factors
If kept in place, 3 months of anticoagulation

Antineoplastic Therapy

Adjuvant chemotherapy for breast cancer has been associated with an increased risk of both arterial and venous thromboembolism (in 5–7% of patients) [81]. The thrombogenic stimulus is not clear, but this could reflect vascular damage by the chemotherapeutic agents or perhaps a reduction in natural anticoagulants, such as protein C or protein S concentrations.

L-Asparaginase – an effective therapy for acute lymphocytic leukemia – is associated with thrombosis [82, 83]. The overall rate of thrombosis in children is 5% but may be as high as 36% if asymptomatic thromboses are included and can range from 5% to 20% in adult. The rate of potentially devastating CNS thrombosis is approximately 1–2% of patients with childhood ALL and up to 4% of adults. Thrombosis usually occurs 2–3 weeks after the start of a course of therapy. Most patients recover, although serious neurologic defects or even death can occur.

The pathogenesis of the thrombotic complications of L-asparaginase may be related to decreased levels of natural anticoagulants antithrombin III, protein C, protein S, and plasminogen via general inhibition hepatic protein synthesis by L-asparaginase.

Patients with acute thrombosis should have levels of fibrinogen and antithrombin drawn before anticoagulation and if deficient supplemented to keep fibrinogen greater than 150 mg/dL and antithrombin greater than 80%. Platelets need to be kept greater than 50 × 109/L during acute anticoagulation.

There remains no consensus on prevention of thrombosis given varying results of clinical trials. There is increasing evidence that LMWH prophylaxis at either 40 mg/day or 1 mg/kg/day is effective at preventing thrombosis [84].

The anti-myeloma agents thalidomide and lenalidomide are both associated with substantial rates of thrombosis that can be as high as 36–75% [85]. The incidence is higher with the use of dexamethasone and with chemotherapy, especially doxorubicin. These agents may have a direct toxic effect on the vascular endothelium promoting a prothrombotic state. Aspirin appears useful for thrombosis prevention in low-risk patients, while those who have had previous thrombosis, receiving dexamethasone or chemotherapy, or have central lines may benefit from warfarin or LMWH prophylaxis.

Targeted antineoplastic therapy also increases the risk of thrombosis. Bevacizumab has been associated with a ~two-fold increase in arterial thrombosis [86] but not venous disease [87]. This may be a class effect of VEGF inhibition as the VEGF tyrosine kinase inhibitors such as sorafenib and sunitinib also increase arterial thrombosis 2.2-fold [88]. Several of the new tyrosine kinase inhibitors developed for treatment of chronic myelogenous leukemia also increase the risk of arterial thrombosis – the most pronounce risk with ponatinib with an incidence ratio of 40.7 per 100 patient years [89, 90].

Use of Anticoagulants in Thrombocytopenic Patients

A common issue for which there is little guidance is management of anticoagulation in patients who are or are at risk of becoming thrombocytopenic [91, 92]. For venous thrombosis, full-dose heparin/DOAC can be given to a platelet count of 50,000/uL and prophylactic dosing down to 20 × 109/L [93]. Aspirin given for primary prevention can be held until therapy is over. For secondary prevention, one would hold aspirin when platelets decrease to under 50 × 109/L. For acute coronary events, patients should receive aspirin no matter what their platelet counts are [94].

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Infectious Disease

38

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Introduction

While the emergency physician specializes in evaluating and managing patients with undifferentiated illness, those with cancer and undergoing treatment represent a unique challenge due to their immunocompromised state, lack of typical inflammatory signs and symptoms, and atypical clinical presentations. In such cases, fever may be the only presenting symptom of infection; however, even lack of fever cannot preclude an infectious disease emergency. Malignancies and their treatment modify immune defenses in many ways, and frequent healthcare interventions, including central venous catheterization, further add to the risk of infection. Cytotoxic chemotherapy often results in disruption of mucosal barriers and reduction in functional neutrophils, both of which are critical components of the innate immune system.

Febrile neutropenia in a patient with cancer is an oncologic emergency. While many advances have been made in prevention and management of febrile neutropenia syndromes, infection remains a serious cause of morbidity and mortality in oncologic patients. Major complications (e.g., hypotension, acute renal failure, respiratory failure) in the context of febrile neutropenia occur at a rate of approximately 25–30% with mortality rates as high as 11%; in the setting of severe sepsis or septic shock, mortality can approach 50% [1–3]. Rapid assessment and timely interventions, including the initiation of empiric antibiotics, can be crucial in preventing complications and deterioration in a patient's clinical course. Therefore, emergency physicians must maintain a high index of suspicion for infection in any oncologic patient presenting to the emergency department (ED) with acute illness.

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Risk Factors and Immune Compromise

Oncologic patients have many risk factors for infection. Malignancy frequently causes immune compromise, particularly those malignancies affecting the hematopoietic system. Cancers can be inflammatory, releasing cytokines resulting in disordered immune responses. Primary or metastatic tumors can result in anatomic defects promoting infection, such as an endobronchial lesion predisposing a patient to post-obstructive pneumonia. Furthermore, many cancer treatments result in unintended adverse effects, including neutropenia and mucositis. Surgical interventions and procedures, such as port placement, can be complicated by subsequent infection. Due to immune impairment, many oncologic patients may lack classic symptoms of infection (e.g., fever, signs of inflammation). Therefore, a strong clinical suspicion for infection should be maintained during assessment of the acutely ill oncologic patient presenting for ED care.

The spectrum of infectious diseases seen in oncologic patients can be broadly categorized based on primary immune dysfunction (Table 38.1) [4, 5]. For example, patients with primary neutropenia are most susceptible to infection from bacteria they are already colonized with or those found in their environment. These patients frequently develop bacteremia from gastrointestinal pathogens (due to gut translocation), oral pathogens (due to mucositis), or skin flora (due to skin breakdown and/or sites of central venous access). They are also at high risk for infection due to fungi, including *Candida*, *Aspergillus*, and other molds [4].

Patients who have lymphomas, those receiving T-cell-targeting therapies, or those taking high-dose steroids are considered to have dysfunction of cellular-mediated

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Table 38.1 Immune defects and their associated pathogens [5]

Immune dysfunction	Associated conditions	At-risk pathogens
Neutrophil defects	Cytotoxic chemotherapy Hematologic malignancy Marrow infiltration Drug-induced neutropenia	Bacteria: *Staphylococcus aureus*, *Viridans streptococci*, *Pseudomonas*, *Stenotrophomonas*, *Enterobacteriaceae*, *Clostridium* Fungi: *Candida*, *Aspergillus*, *Fusarium*, *Zygomycetes*, *Trichosporon*
Cellular immunity defects	Stem cell transplantation Chronic immunosuppressive therapy Hodgkin's lymphoma HIV infection Irradiation	Bacteria: *Mycobacteria*, atypical bacteria (*Nocardia*, *Legionella*, *Listeria*), zoonoses (*Bartonella*, *Brucella*) Fungi: endemic mycoses (*Histoplasma*, *Blastomyces*, *Coccidioides*, *Paracoccidioides*, *Penicillium*), *Pneumocystis jirovecii*, *Cryptococcus*, *Candida*, *Aspergillus* Viruses: herpesviruses (CMV, HSV, VZV, EBV, HHV-6), HPV, community-acquired viral infections Parasites: *Toxoplasma*, *Strongyloides*, *Leishmania*, *Cryptosporidium*
Humoral immunity defects	Drug-induced B-lymphocyte depletion Splenectomy or functional asplenia Hematopoietic stem cell transplantation Paraproteinemias Non-Hodgkin's lymphoma	Bacteria: *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Capnocytophaga* (particularly if receiving rituximab or alemtuzumab) Viruses: Enteroviruses Parasites: *Giardia*, *Plasmodium*, *Babesia*

CMV cytomegalovirus, *HSV* herpes simplex virus, *VZV* varicella-zoster virus [VZV], *EBV* Epstein-Barr virus, *HHV* human herpes virus

immunity. They are particularly vulnerable to infection due to mycobacteria and atypical bacteria, such as *Nocardia*, *Legionella*, and *Listeria*, as well as viruses, including herpesviruses (i.e., cytomegalovirus [CMV], herpes simplex virus [HSV], varicella-zoster virus [VZV], and Epstein-Barr virus [EBV]). They are also more susceptible to infection due to fungi, including dimorphic molds such as *Histoplasma*, *Coccidioides*, and *Blastomyces*, as well as *Pneumocystis jirovecii*, *Aspergillus*, and *Cryptococcus* [4]. Finally, those with therapies targeting B-cells (e.g., monoclonal antibodies against CD-20 surface proteins), hypogammaglobulinemia secondary to malignancy, or those post-splenectomy are considered to have deficits of humoral immunity, placing them at increased risk for infection due to encapsulated bacteria including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. These patients also have an increased risk of parasitic infection.

Antimicrobial Prophylaxis for Cancer Patients

Prophylactic antimicrobial, antifungal, and antiviral therapies are often employed to mitigate the risk of infection associated with necessary and life-saving cancer treatments. Prophylaxis is tailored to an individual patient's risks and is frequently left to the discretion of the oncologic provider. Hospitals and healthcare systems often have their own internal policies or guidelines, and it is useful to be familiar with these. Herein are the most common oncologic scenarios in which patients receive antimicrobial prophylaxis and the underlying reasoning for doing so. Understanding the rationale for commonly prescribed antimicrobial prophylaxis can help emergency physicians better navigate the differential diagnosis of infection in an acutely ill oncologic patient.

Hematopoietic Stem Cell Transplantation (HSCT)

HSCT is a life-saving procedure for patients with hematologic malignancy. However, this treatment often comes with risk of infection from a variety of pathogens. The process of HSCT (whether allogeneic or autologous) requires a cytotoxic conditioning regimen that produces a period of time in which the patient does not have a completely functional immune system. The degree of immunosuppression will depend on the conditioning regimen and the time it takes to achieve engraftment of stem cells. Further immune compromise is common in allogeneic HSCT patients who suffer from graft-vs-host disease (GVHD). The immunosuppression required to treat this condition often further impairs an already fragile immune system.

The role for prophylaxis in HSCT is well established [6, 7]. Prior to HSCT, the recipient and donor often undergo screening as a means to risk stratify and tailor post-transplant antimicrobial prophylaxis for the recipient. For example, a recipient with existing IgG antibodies to CMV will receive antiviral prophylaxis with a drug that is active against CMV, such as valganciclovir, as opposed to prophylaxis with acyclovir, which targets only HSV and VZV. Likewise, a prior history of invasive mold infection can prompt initiation of mold active antifungal prophylaxis. In general, most prophylaxis is aimed at bacteria commonly found on mucosal surfaces or the gastrointestinal tract (e.g., Gram-negative rods including *Pseudomonas aeruginosa*), fungi (e.g., *Candida*, *Aspergillus*), and herpesviruses.

Table 38.2 Antimicrobial prophylaxis in the HSCT patient

	Pre-engraftment phase	Early post-engraftment phase	Late post-engraftment phase
Pathogens with the greatest risk	Gram-negative bacilli (including *Pseudomonas*), Gram- positive cocci, HSV, *Candida* spp., *Aspergillus*	Gram-negative bacilli (including *Pseudomonas*), Gram-positive cocci, HSV, CMV, *Candida* spp., *Aspergillus*	Encapsulated bacteria, VZV, *Aspergillus*, *Pneumocystis jirovecii*
Antibacterial prophylaxis	Fluoroquinolones (ciprofloxacin or levofloxacin)	Penicillin, amoxicillin, or trimethoprim-sulfamethoxazole	Penicillin, amoxicillin, or trimethoprim-sulfamethoxazole
Antifungal prophylaxis	Fluconazole; if increased risk for mold infection, voriconazole, or posaconazole	Fluconazole, trimethoprim-sulfamethoxazole	
Antiviral prophylaxis	Valacyclovir; if CMV IgG positive, valganciclovir	Valacyclovir vs valganciclovir	Valacyclovir – many institutions continue for 1 year

HSCT hematopoietic stem cell transplantation *CMV* cytomegalovirus virus, *HSV* herpes simplex virus, *VZV* varicella-zoster virus

Infectious risk for patients is often dependent on their phase of recovery following HSCT (Table 38.2). In the pre-engraftment phase immediately post-transplantation, typically the first 30 days, patients are in various stages of engrafting new stem cells. Patients are generally profoundly neutropenic and often have mucosal barrier disruption. Studies have suggested that antimicrobial prophylaxis with fluoroquinolones (ciprofloxacin or levofloxacin) can reduce the rate of infections with Gram-negative organisms [8, 9]. During this neutropenic phase, HSCT patients also have a risk of invasive fungal infection, most notably with *Candida*. Antifungal prophylaxis is often targeted toward *Candida*, consisting of daily fluconazole. However, some institutions and/or protocols may favor the use of antifungals such as voriconazole or posaconazole with expanded mold coverage depending on the type of transplant and expected duration of neutropenia. Antiviral prophylaxis is typically directed against human herpesviruses.

A brief discussion of risk for CMV reactivation is worthwhile, as this may seem counterintuitive in HSCT. A high-risk patient is a recipient who is CMV IgG positive at the time of transplant [10]. This high-risk status exists regardless of the donor's status; however, a stem cell transplant from a CMV IgG-positive donor may be protective. As CMV infection is typically a disease of reactivation in HSCT, transplantation from a seronegative donor into a seropositive recipient effectively provides a high-risk recipient with an immune system that has not previously encountered CMV. Various strategies for the management of CMV reactivation exist. Some institutions surveille for reactivation and then provide treatment as needed. Frequently, institutions provide pre-emptive CMV prophylaxis based on recipient seropositive status [11]. Valganciclovir [12] and letermovir [13] have been demonstrated to reduce the risk of CMV disease in seropositive HSCT patients.

Engraftment of the transplant is evident when the patient is able to maintain a neutrophil count from their own hematopoiesis. Despite the development of improved (and sometimes normal) neutrophil counts, HSCT patients remain immunosuppressed due to impaired activity of B-cells and T-cells. This impaired immune function can last for years in allogeneic HSCT patients. The early post-engraftment phase is often arbitrarily defined as the time of engraftment around day 30 until day 100. Following engraftment, antimicrobial prophylaxis targets encapsulated bacteria, particularly *S. pneumoniae* [6]. Based on local protocols, patients may continue on fluoroquinolones, trimethoprim-sulfamethoxazole, or penicillin. The benefit of trimethoprim-sulfamethoxazole is that it also serves as prophylaxis against *P. jirovecii*, a pathogen known to affect HSCT patients [14]. *P. jirovecii* prophylaxis is generally started after engraftment due to concern for bone marrow suppression with trimethoprim-sulfamethoxazole. Antifungal prophylaxis against *Candida* is typically continued during this phase for up to 75–100 days [15].

The late post-engraftment phase refers to the period of time from 100 days until 1-year post-transplant. In this phase, cellular immunity remains impaired. Antibiotic prophylaxis against encapsulated bacteria, specifically *S. pneumoniae*, is typically continued for up to a year. There is evidence to support the role of prophylaxis against HSV and VZV for up to a year to prevent infection [16]. Currently, CMV prophylaxis is not recommended in the late post-engraftment phase [17].

Graft-vs-host disease (GVHD) occurs when transplanted immune cells (from the stem cell transplant) react to recipient tissues. Manifestations of GVHD vary among HSCT recipients. Treatment of GVHD often consists of steroids and frequently escalates to involve immunosuppression with JAK inhibitors or calcineurin inhibitors. In patients with GVHD, prophylaxis often intensifies based on patient risk factors. Some institutions transition antifungal coverage to include mold coverage, if the patient was not already on this. There is some data to suggest that in GVHD, posaconazole and, theoretically, voriconazole decrease the risk for invasive aspergillosis and death [18]. Antibiotic prophylaxis is often continued and will include trimethoprim-sulfamethoxazole for *P. jirovecii* prophylaxis. Antivirals will continue as previously prescribed. In patients with GVHD, antimicrobial prophylaxis often continues until immunosuppression is decreased.

Chemotherapy-Induced Neutropenia

Cytotoxic chemotherapy is a frequent cause of bone marrow suppression and subsequent neutropenia. The risk of infection associated with neutropenia is related to the severity (i.e., how low the neutrophil count is) and the duration of neutropenia. Severe neutropenia is defined as an absolute neutrophil count less than 500 cells/μL. Patients with severe neutropenia for a duration of more than 7 days are considered to be high risk for infection.

Recent guidelines suggest that prophylaxis for neutropenia should be targeted and based on the patient's risk for neutropenia-related infection [19]. For patients with risk of severe neutropenia, current evidence suggests benefit with fluoroquinolone antibiotic prophylaxis [20, 21]. Levofloxacin is often preferred due to its spectrum of activity against *Streptococci* and *P. aeruginosa*. Ciprofloxacin may also be considered. Antifungal prophylaxis with fluconazole, or other triazoles, is recommended in patients who are expected to have severe neutropenia [19]. Prophylaxis against *P. jirovecii*, with trimethoprim-sulfamethoxazole, is also recommended if the risk of *Pneumocystis* pneumonia is felt to be high (typically based on use of high-dose corticosteroids or purine analog therapy) [19]. Of note, use of trimethoprim-sulfamethoxazole alone as prophylaxis against *Pneumocystis* and bacterial pathogens is not recommended due to their limited spectrum of activity compared to fluoroquinolones.

Chemotherapy and Immunotherapy Against Solid Organ Tumors

Though chemotherapy for treatment of solid organ tumors risks depressing the immune system, routine prophylaxis is generally not given. Based on current guidelines, the decision to use fluoroquinolones for prophylaxis in solid organ tumor patients receiving cytotoxic chemotherapy with severe neutropenia should be made on a case-by-case basis [22]. In patients who will be treated with high-dose steroids (≥20 mg of prednisone daily for ≥4 weeks), consideration should be given to *P. jirovecii* prophylaxis using trimethoprim-sulfamethoxazole. Newer immune system-modulating therapies used in cancer treatments may promote risk for invasive infections [23]. Adverse effects of these medications are frequently treated with immune-suppressing therapies (such as corticosteroids). At this time, no guidance on routine prophylaxis before their use exists.

Evaluation of the Oncologic Patient with Infection

When approaching care of the acutely ill oncologic patient in the ED, providers must decipher signs and symptoms that frequently overlap infectious and malignant syndromes. While a fever in an oncologic patient usually indicates infection, it may also result from medications, venous thromboembolism, or the malignancy itself [24].

Fever can be a paraneoplastic syndrome in a wide range of tumor types, from hematologic cancers such as lymphoma and leukemia to solid cancers such as renal cell carcinoma, glioblastoma multiforme, and ovarian carcinoma [25]. While the exact mechanisms of how malignancy induces fever are not fully understood, it is theorized that the release of pyrogenic cytokines directly from tumor cells, or from macrophages responding to the tumor, can induce prostaglandin E2, which acts on the hypothalamus and causes a change in the thermostatic set point. These cytokines – IL-1, IL-2, IL-6, IL-12, TNF, and interferon – also play a crucial role in driving the inflammatory response to infection [25, 26]. Other theories have focused on activation of cytokines by mutated receptors such as RAS; and IL-6 levels are often associated with driving outcomes in lymphomas and renal cell carcinoma [27]. Because the inflammatory states of both neoplastic and infectious origins share similar cytokines, clinical presentations may be indistinguishable between the two, requiring a careful and thorough workup to differentiate them. However, there are differences in the clinical features of fever caused by malignancy compared to infection (Fig. 38.1). Systemic signs and symptoms such as rigors, chills, tachycardia, or hypotension are often muted with malignancy compared to infectious fever. Further, neoplastic fevers are often not relieved by acetaminophen [27].

When approaching a fever of unclear etiology, the first priority of the emergency physician is to treat any presumed underly-

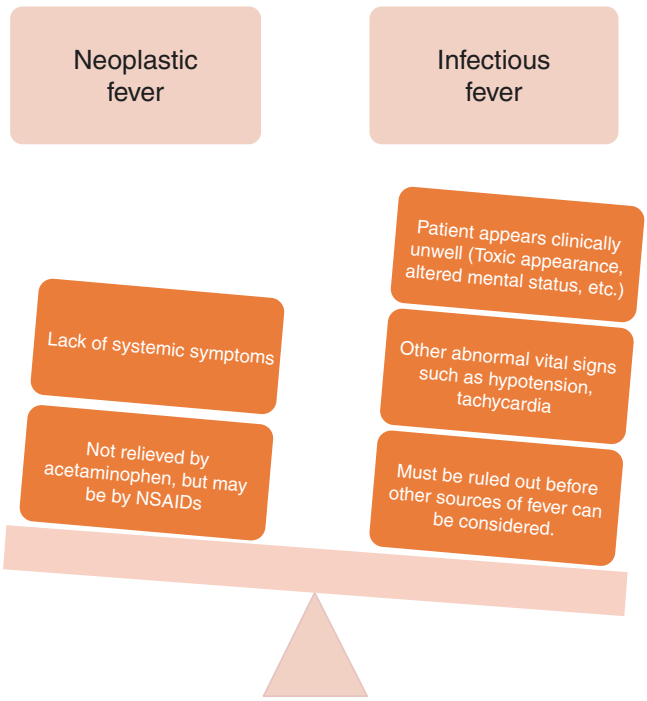

Fig. 38.1 A comparison of neoplastic and infectious fever

ing infection. A fever of unclear etiology in an oncologic patient should be treated as infectious until proven otherwise based on careful examination, laboratory data, and imaging. Neoplastic fever should only be considered once other diagnoses have been thoroughly excluded. The evolving story of SARS-CoV-2 is covered in a separate chapter of this text.

Febrile Neutropenia: An Oncologic Emergency

A frequently encountered syndrome in patients receiving cytotoxic chemotherapy (and sometimes in patients with hematologic malignancies) is neutropenic fever, which is considered an oncologic emergency. This is defined as a temperature ≥38.3 °C once or ≥38.0 °C sustained over an hour in the setting of absolute neutrophil count (ANC) <500 cells/μL or an ANC <1000 with predicted nadir <500 cells/μL [28]. Neutropenic fever requires prompt evaluation and empiric antimicrobial treatment as indicated. The choice of antibiotics and location of treatment is based on underlying risk factors [22, 28]. Patients with comorbid conditions, those with severe neutropenia (ANC <100 cells/μL), and those with neutropenia that will last ≥7 days are at greatest risk for febrile neutropenia.

History and Physical Examination

A careful review of the patient's history and a thorough physical examination should be undertaken. When evaluating an oncologic patient in the ED, it is helpful to sort out the following information:

- Location of the tumor and/or metastases with attention to potential anatomic changes as a result (e.g., does the patient have metastases that could cause urinary, respiratory, bowel, or biliary obstruction?)
- What foreign objects does the patient have inside them (e.g., do they have a central venous catheter, implantable port, urinary catheter, drain, or other implantable device?)
- What therapies are being used to treat the patient and when did he/she last receive them? (e.g., did the patient receive outpatient chemotherapy or are they receiving immunotherapy?)
- What infections has the patient had and/or what infections are they currently being treated for? (e.g., does the patient have a history of a multidrug-resistant organism? Are they currently receiving antimicrobial prophylaxis?)
- What other comorbidities (e.g., diabetes, end-stage renal disease) does the patient have that may increase their risk for infection or worsen clinical outcomes?

While these points do not constitute all of the history that should be obtained, they can help narrow the differential diagnosis. A thorough physical examination can also elucidate supporting signs and symptoms for a suspected infection. Assessing the patient's overall clinical appearance can be the first step in establishing a clinical gestalt – does the patient appear sick or unwell? Has there been a change from their baseline mental status? Central venous catheters, implantable ports, and surgical sites should be inspected for any signs of infection that could lead to bacteremia or wound infection. A tender, distended abdomen in a patient with liver cancer and ascites can suggest peritonitis. Decreased breath sounds and rales in a lung cancer patient may indicate a developing pneumonia or empyema. Early determination of these factors can help guide initial management, including administration of fluids and empiric antibiotics, and inform clinical decision-making regarding the need for imaging.

Initial Diagnostic Workup

All patients with known malignancy and fever require a full infectious workup (Fig. 38.2). Though most patients with neutropenic fever may never have a diagnosed etiology, all patients presenting with febrile neutropenia should be treated as if they have true infection. After 48–72 h of continuous fever without positive culture data or response to antibiotics, alternative infectious etiologies should be considered including less common fungal, viral, and parasitic organisms.

Initial workup of an oncologic patient presenting with fever should include but is not limited to:

- Thorough history and physical examination to identify possible infectious sources including wounds, surgical sites, and indwelling central venous catheters and urinary catheters
- Complete blood count with differential, complete metabolic panel including hepatic function panels, other electrolytes, and serum lactate
- At least two sets of blood cultures from different sites, with consideration of obtaining a set from current indwelling central venous catheter or implantable port (if there is concern for infection involving the device)
- Microbiologic cultures from other sites including sputum, tracheostomy tubes, wounds, surgical incisions, CSF, and stool as applicable
- Urinalysis and urine cultures
- Chest radiography for the patient presenting with hypoxia, new oxygen requirements, or respiratory symptoms
- Brain imaging and lumbar puncture in a patient with altered mental status or neurological symptoms

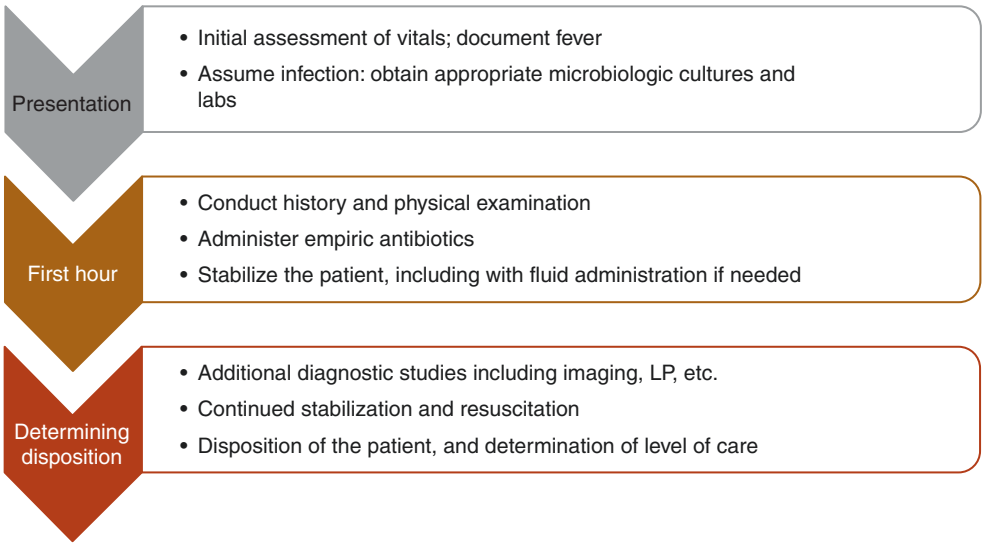

Fig. 38.2 An approach to evaluation of the oncologic patient with neutropenic fever and/or suspected infection in the emergency department

Table 38.3 MASCC risk assessment [29]

Factors	Score
Burden of disease	
No or mild symptoms	5
Moderate symptoms	3
Severe symptoms	0
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy without previous fungal infection	4
No dehydration	3
Outpatient status at onset of fever	3
Age of <60 years	2
Total score of 21 or higher means that the patient is considered as low risk for complication	

MASCC Multinational Association for Supportive Care in Cancer

- Nasopharyngeal swabs for patients with flu-like symptoms in the setting of community-acquired respiratory illnesses such as influenza or COVID-19

Ideally, patient assessment should be performed as soon as possible as delays in treatment can adversely affect outcomes. The goal of the emergency physician is not to identify a specific infectious diagnosis, but to maximize the chances of establishing clinical and microbiologic diagnoses later in the patient's clinical course that may affect treatment, including antibiotic choice and prognosis. In this same vein, the emergency physician must assess the patient's risk for infectious complications. Different risk stratification scoring systems have been proposed – the Multinational Association for Supportive Care in Cancer (MASCC) score is based on seven clinical factors derived and validated from prospective analyses (Table 38.3) [29].

While low-risk patients may be considered for outpatient therapy, high-risk patients will most likely require empiric intravenous antibiotics and hospitalization. Identifying a patient's risk for infectious complications is an important skill for the emergency physician as it ultimately determines the disposition of the patient and the level of care they will receive during their hospital course.

Treatment and Management

Guidelines from the American Society of Clinical Oncologic (ASCO) and Infectious Diseases Society of America (IDSA) for empiric treatment recommend the early use of broad-spectrum antibiotics when treating febrile neutropenia [22, 28]. Stabilization of the sick patient is the critical goal for the emergency physician. Early aggressive fluid resuscitation should be considered in patients presenting with sepsis and/or septic shock. Early blood products may also be required due to the marrow suppressing nature of cytotoxic chemotherapy. Obtaining central venous access, if not already present, and initiating vasopressor therapy can be crucial in preserving hemodynamics. Source control through removal of an infected central venous catheter or urinary catheter or drainage of an infected fluid collection (e.g., abscess) may be necessary. Early communication with the patient's oncologist or an on-call oncologist can help facilitate disposition and ensure proper next steps in management and follow-up.

Gram-positive or Gram-negative bacteria account for more than 90% of the causes for a first febrile episode in neutropenic patients [4]; therefore, empiric antibiotic regimens must be broad-spectrum and bactericidal and achieve therapeutic levels quickly (Fig. 38.3). Based on IDSA guidelines, patients should receive at least monotherapy with an antibiotic that empirically covers *P. aeruginosa* [28]. Reasonable choices therefore include an anti-pseudomonal fourth-generation cephalosporin (cefepime), β-lactam/β--

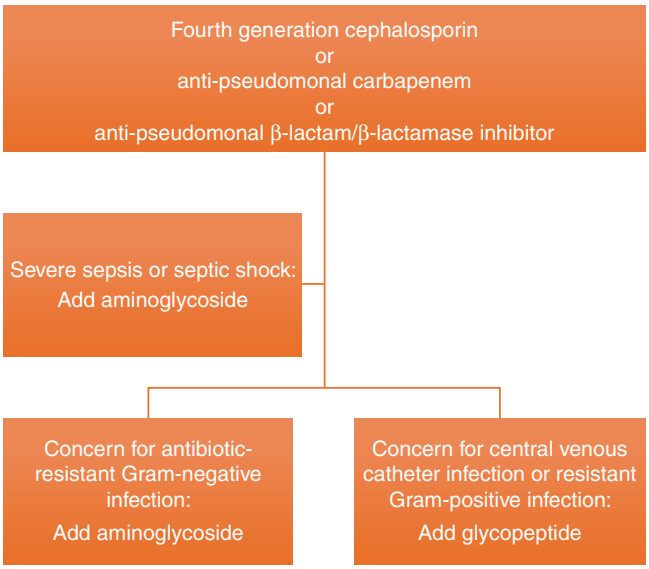

Fig. 38.3 Empiric antibiotic therapy for suspected infection in high-risk oncologic patients

lactamase inhibitor (piperacillin-tazobactam), or carbapenem (meropenem). Vancomycin, or other agents targeted against resistant Gram-positives (linezolid, daptomycin), should be considered in patients who have suspected central venous catheter infection or severe skin and soft tissue infection. Septic patients may also require treatment with an aminoglycoside, especially when there is a history of resistant Gram-negative infection. Additional empiric coverage directed toward fungi and viruses can be considered based on the clinical context (e.g., previous fungal infection, previous isolation of multidrug-resistant organisms) and local antibiogram data [28].

Recent ASCO/IDSA guidelines have outlined a population of patients who may be safely treated for neutropenic fever outside of the hospital setting. Again, validated tools such as the MASCC index or the Clinical Index of Stable Febrile Neutropenia (CISNE) can aid decision-making [29, 30]. In stable, low-risk patients felt to be candidates for outpatient treatment, the current recommended antibiotic regimen includes fluoroquinolones active against *Pseudomonas* plus amoxicillin/clavulanate or clindamycin [22].

Case Study 1: An Oncologic Patient with Fever and Neutropenia

A 62-year-old woman with hypertension, COPD, and diffuse large B-cell lymphoma presents to the ED via *private vehicle with fever. She first felt "hot" earlier this morning and found her temperature to be 102 °F. She has not had any other symptoms and feels well overall. She completed her first cycle of chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) 2 weeks ago. She does not report any recent travel.*

On arrival to the ED, the patient's vital signs are notable for a temperature of 102.5 °F, a heart rate of 98 beats per minute, and a blood pressure of 88/60 mmHg. A head-to-toe physical examination finds a well-appearing female with clear lung sounds, a non-tender abdomen, and good pulses in all her extremities. Initial laboratory assessment demonstrates a hemoglobin of 12.1 mg/dL and a white blood cell count of 1700 cells/μL. The laboratory calls the emergency physician with a critical lab result from the white blood cell differential – the absolute neutrophil count is 200 cells/μL. Given concern for neutropenic fever, the emergency physician obtains two sets of blood cultures and a urine culture and starts the patient empirically on intravenous cefepime, all within 1 h of her presentation to the ED. A chest radiograph shows no evidence of pneumonia and a urinalysis is within normal limits. The emergency physician determines that the patient is at high risk for infectious complications with a MASCC score of 15. She notifies the oncologist of the patient's neutropenic fever and recommends admission for further workup and observation. The oncologist concurs and is appreciative of the call.

During the hospitalization, the patient's blood and urine cultures show no growth. The oncologic team decides to administer granulocyte colony-stimulating factor. Three days later, her fever has resolved, and her absolute neutrophil count has increased to 500 cells/μL. She is discharged on oral ciprofloxacin and amoxicillin/clavulanate and is scheduled follow-up in 2 days with her oncologist. This case demonstrates the importance of early recognition of neutropenic fever, appropriate microbiological culture collection, and prompt initiation of empiric antibiotics, even in the absence of other localizing symptoms. Risk stratification tools such as the MASCC score and close communication with a patient's oncologist can help in clinical decision-making and securing timely outpatient follow-up once the patient has been discharged.

Special Considerations

Syndromic Approaches

Specific history and physical examination findings can help one to narrow their approach when diagnosing the cause of a fever in an oncologic patient. The following is a brief review of specific clinical syndromes and how one might approach them when it comes to infection.

Pulmonary syndromes usually manifest by increased work of breathing, hypoxia, and cough with or without sputum production. In neutropenic or stem cell transplant patients, pneumonia carries a high rate of mortality. Infiltrates

may not be prominent on routine chest radiography; thus computed tomography should be obtained in those who have clinical symptoms but a seemingly clear chest x-ray. Bacterial pathogens, such as *S. pneumoniae*, *Staphylococcus aureus*, and *P. aeruginosa*, predominate as causes of pneumonia in immunosuppressed oncologic patients [31, 32]. Given their frequent encounters with healthcare, resistant Gram-negative organisms are also frequently isolated, including *Stenotrophomonas maltophilia*, *Acinetobacter* spp., *Klebsiella pneumoniae*, etc. [31]. A high index of suspicion must also be maintained for fungi such as *Aspergillus* spp. and *P. jirovecii* [32]. In immunosuppressed patients, community respiratory viruses can cause pulmonary infiltrates on chest x-ray and result in significant morbidity. Influenza, respiratory syncytial virus, parainfluenza, and SARS-CoV-2 are among the many circulating viruses that can cause serious respiratory syndromes. Assessment should include routine labs and sputum culture, if the patient is making sputum. In critically ill patients who do not respond to empiric antibiotic therapy, bronchoalveolar lavage with microbiologic culture can help further guide coverage.

Skin and soft tissue infections have a broad differential in the immunosuppressed patient. The classic erythema, pain, warmth, and swelling of cellulitis may be less prominent than in immunocompetent patients. Clinicians should have a high index of suspicion for necrotizing infections, especially when patients have significant pain out of proportion to the exam. It is also important to recognize that in neutropenic or immunosuppressed patients, skin lesions are frequent manifestations of disseminated disease [5]. When evaluating skin infections, it is important not to overlook mucous membranes, which may help to differentiate cutaneous syndromes vs. systemic processes (such as disseminated viral processes). Vesicular, crusted, or shallow ulcerative lesions may suggest a viral process, such as disseminated zoster or herpes simplex virus. Nodular lesions may be suggestive of fungal or mycobacterial processes. Erythematous skin lesions with central necrosis can also signify a fungal process. Unfortunately, many non-infectious processes, including Sweet's syndrome, can mimic cutaneous infection. The diagnosis of these infections often relies on not only routine laboratory tests and blood cultures but frequently skin biopsy for pathology and special stains (e.g., Gram stain, GMS stain, Fite stain).

Gastrointestinal syndromes manifest as abdominal pain, nausea, vomiting, and diarrhea. Given their frequent exposure to healthcare and antibiotics, oncologic patients are at increased risk for *Clostridioides difficile* infection [33]. They are also at risk for a range of bacterial infections, including *E. coli*, *Salmonella*, *Shigella*, and *Campylobacter* [34]. Viral (CMV, norovirus) and parasitic (e.g., *Cryptosporidium*, *Strongyloides*, *Entamoeba*) causes should also be considered in immunosuppressed patients with unexplained diarrhea. Typhlitis is a life-threatening condition due to neutropenia resulting in necrotizing enterocolitis, predominantly affecting the cecum. This most often manifests as right lower quadrant abdominal pain, many times with associated bloody diarrhea [35]. This can be readily diagnosed on CT scan. Patients who have pain or difficulty swallowing should be evaluated for esophagitis, which may be due to *Candida*, CMV, or HSV infection. The approach to an immunosuppressed patient with abdominal pain often includes routine laboratory tests, including liver function testing, pancreatic enzymes, and stool studies (for *C. difficile* toxin or polymerase chain reaction, fecal leukocytes, and stool culture). When patients have significant pain, early CT scan should be considered. It should be noted that oncologic patients are also at risk for non-infectious causes of gastrointestinal illness, including tumor effects, medication effects, and, in HSCT patients, gastrointestinal graft-vs-host disease.

Central nervous system infections should be considered not only in patients with classic meningeal symptoms but also in those who are altered or obtunded. Emergency physicians should have a low threshold for evaluating patients for neurologic infections. Patients with symptoms concerning for focal neurologic deficits or meningoencephalitis should undergo imaging and early lumbar puncture as indicated, with appropriately recorded opening pressure. In addition to typical meningitis pathogens, such as *S. pneumoniae*, *H. influenzae*, and *Neisseria meningitidis*, immunosuppressed oncologic patients are at increased risk of infection due to pathogens such as *Listeria monocytogenes*, *Cryptococcus neoformans*, and herpesviruses (HSV/VZV) [35]. Those with a history of neurosurgical procedures have an increased risk for coagulase-negative staphylococci, *S. aureus*, and Gram-negative rods [36]. Early pathogen identification can improve time to life-saving therapies. Intracranial mass lesions can have many etiologies, including bacterial abscess, fungal infection, or *Toxoplasma*. The workup for these will often depend on imaging characteristics. Fungal sinusitis is a diagnosis that can mimic a neurologic syndrome based on severe headache and ocular nerve palsies. This is a diagnosis not to miss as the associated mortality is very high [37].

Healthcare-associated infections can arise from any number of interventions associated with cancer care. Central venous catheters and implantable ports are frequently used to provide chemotherapy, intravenous fluids, blood product transfusions, and other treatments. A central line-associated bloodstream infection (CLABSI) is defined by the Centers for Disease Control and Prevention as a primary bloodstream infection in a patient who has had a central venous catheter in place for more than 48 h with a bacterial or fungal pathogen isolated from one or more blood cultures unrelated to another source of infection [38]. While surveillance and clinical definitions may vary, a CLABSI can contribute significant morbidity and mortality, particularly in patients who

have undergone HSCT [39, 40]. Coagulase-negative staphylococci, *S. aureus*, *Enterococcus faecium*, *E. coli*, and *Candida* are common causative organisms, with antibiotic-resistant organisms increasingly implicated [41, 42]. Fever, chills, and rigors may not always be present, particularly with infection due to coagulase-negative staphylococci. Erythema, induration, and purulence at the insertion site for the central venous catheter or overlying the pocket of an implantable port should raise suspicion that this device could be a potential source of infection. At least two sets of blood cultures should be obtained preferably from two separate peripheral sites; one set can be drawn from the central venous catheter or implantable port when necessary. When clinical suspicion for CLABSI or implantable port infection is high, device removal is preferred [42, 43]; this decision should be made in consultation with the patient's oncologist. Presence of an indwelling urinary catheter in an oncologic patient presenting with fever, suprapubic tenderness, costovertebral angle tenderness, or urinary symptoms should raise concern for a catheter-associated urinary tract infection (CAUTI). Urinalysis and urine culture help establish the diagnosis and guide antibiotic therapy; catheter removal is strongly recommended. Avoidance of unnecessary urinary catheterization, including in the ED, should remain a major strategy to prevent CAUTI [44].

Case Study 2: A Thorough Examination Uncovers the Source of Fever in an Ill Oncologic Patient

A 73-year-old man with hypertension, coronary disease, and small-cell lung cancer presents to the ED via *emergency medical services for altered mentation and hypotension. Approximately 12 h prior to admission, the patient developed fever at home, and his mental status subsequently declined throughout the day. His wife eventually called EMS and on arrival he is obtunded and hypotensive.*

In the ED, the patient is febrile to 101.3 °F with a heart rate of 120 beats per minute and a blood pressure of 73/29 mmHg. A head-to-toe physical examination is performed. He is obtunded but has no focal deficits and is protecting his airway. His heart and lung exam are significant for crackles in the lung bases. Abdominal examination is benign. On exposure of the chest during a complete skin examination, mild erythema and induration are visualized overlying the site of his implantable port. Initial laboratory assessment demonstrates anemia (hemoglobin 9.7 mg/dL), thrombocytopenia (platelet count 129 × 10^9/L), and a white blood cell count of 6000 cells/μL. Two sets of blood cultures are obtained, and the patient is started empirically on intravenous vancomycin. A central venous catheter is placed and vasoactive agents are started. It is noted the patient recently completed cycle 3 of cisplatin and etoposide for his cancer. He has not had any recent procedures.

The patient is admitted to the oncologic ICU. Twelve hours into his stay, blood cultures are reported as positive for Gram-positive cocci in clusters. The following day, his implantable port is removed. The organisms in blood cultures are identified as methicillin-resistant Staphylococcus aureus. Two days later, he is improved and able to transition out of the ICU. This case demonstrates the importance of a thorough physical examination in identifying potential sources of fever in an oncologic patient, including evaluation of vascular access devices commonly used for cancer treatment.

Future Issues and Considerations

In the United States, there are over 14 million people who have been treated for cancer sometime during their life [44]. While outpatient therapy is the mainstay of cancer management, the ED is the first destination for many patients with acute complications. National data suggests that patients with cancer make up approximately 3% of all ED visits with an admission rate that is much higher than that of the general ED population; future studies should focus on improving emergency care, especially with regard to febrile neutropenia [45]. As stated before, guidelines recommend early administration of empiric antibiotics for patients who present with neutropenic fever. However, in the setting of ED overcrowding and prolonged boarding times, significant delays in initiating treatment have been observed, with some studies reporting a median time to initial antibiotics ranging from 102 to 300 min [46]. Understanding the barriers that prevent prompt treatment and care can provide systemic targets for improving overall patient flow in the ED. Another consideration is the continued efforts to develop risk stratification methods to identify patients with the highest risk of serious infection and need for immediate assessment. As protocols and systems have developed to improve intervention times of other emergent presentations such as myocardial infarction and stroke, similar systems can be developed to reduce the time to initial antibiotic treatment. However, these strategies must be based on adequately powered and valid studies with convincing evidence of positive clinical effects and outcomes [45].

As physicians wage a never-ending arms race against evolving multidrug-resistant bacteria, it is important to consider the potential ramifications of continuing broad-spectrum antibiotics when it comes to antibiotic stewardship. While inadequate antibiotic treatment can lead to worse clinical outcomes in oncologic patients, continued use of broad-spectrum therapy when not indicated promotes selection of antibiotic-resistant bacteria. As the use of antibiotics has evolved over time, causative organisms associated with

febrile neutropenia have shifted from Gram-negative bacteria in the 1960s and 1970s to Gram-positive bacteria in the 1980s and now to antibiotic-resistant Gram-negative and Gram-positive bacteria in recent years [47]. Multidrug-resistant organisms including *K. pneumoniae, P. aeruginosa*, and MRSA are associated with considerable mortality in patients with and without neutropenia, although data regarding oncologic patients is limited [48]. Risk assessment for multidrug-resistant infection should be considered for every oncologic patient, particularly those with a history of frequent hospital admissions. While empiric broad-spectrum antibiotic therapy is warranted in the management of undifferentiated infection in a cancer patient, emergency physicians have an important role to play in promoting antibiotic stewardship through responsible prescribing. Selecting the right *d*rug (targeting the most likely organisms with as narrow a spectrum as allowable; using hospital antibiograms to guide antibiotic selection based on trends in local antibiotic resistance), administering that drug at the right *d*ose (e.g., accounting for hepatic and/or renal clearance) for the right *d*uration (shortest time needed to appropriately treat the infection), enabling opportunities to *d*e-escalate antibiotic therapy based on microbiologic cultures, and making sure a drug is prescribed for the right *d*iagnosis in the ED (avoiding antibiotic use when a viral infection is suspected) constitute the 5 Ds of antibiotic stewardship in emergency medicine [41].

Summary and Key Points

The oncologic patient presents a diagnostic challenge to the emergency physician due to their immunocompromised state, lack of typical inflammatory signs and symptoms, and potential for atypical clinical presentations. Fever in a neutropenic patient is an oncologic emergency that necessitates immediate, thorough assessment and early, empiric treatment. When evaluating these patients, the following key points should be remembered:

- Neutropenic fever is defined as a temperature ≥38.3 °C once or ≥38.0 °C sustained over an hour in the setting of absolute neutrophil count (ANC) <500 cells/μL or an ANC <1000 with predicted nadir <500 cells/μL.
- Malignancies can also cause fever, but all fevers must be treated as infectious until proven otherwise.
- Understanding the rationale for antimicrobial prophylaxis in a cancer patient can help narrow the diagnostic possibilities when ill oncologic patients present to the ED.
- A thorough history and physical examination can help uncover subtle signs and symptoms of infection.
- A broad workup should be performed to help maximize the chances of establishing a clinical and microbiological diagnosis.
- Blood cultures should be obtained and empiric broad-spectrum antibiotics started within 1 h of presentation.
- Validated tools such as the MASCC index or the Clinical Index of Stable Febrile Neutropenia (CISNE) can help with risk stratification and determination of disposition.
- Future studies should focus on improving time to antibiotics, risk stratification, and addressing the growing challenge of multidrug-resistant bacteria.

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Febrile Neutropenia

39

Christopher J. Coyne and Rahul V. Nene

Case Study

A 54-year-old female with a history of breast cancer presents to the ED with a low-grade fever (38.3 °C) and myalgias. She denies cough, shortness of breath, chest pain, abdominal pain, dysuria, sore throat, or mouth sores. Her physical exam is non-focal and does not reveal a potential source of infection. The patient has a past medical history of essential hypertension, though is otherwise healthy and exercises every day. Her labs are significant for an absolute neutrophil count of 300 cells/mm^3 and an absolute monocyte count of 600 cells/mm^3. All additional labs including a complete metabolic panel, lactate, and urinalysis are within normal limits. She receives a chest x-ray that is read as negative for acute cardiopulmonary disease. Blood cultures, a urine culture, and a respiratory viral panel are sent and pending.

Given the reassuring clinical picture, the emergency physician applies the Clinical Index of Stable Febrile Neutropenia (CISNE) score to assist with risk stratification. The patient is found to have a CISNE score of zero and is therefore considered low risk of developing severe disease. She is placed in observation status and receives an initial dose of amoxicillin/clavulanate and ciprofloxacin. The patient remains stable for several hours while in the ED. After a discussion between the emergency physician and the patient's primary oncologist, the patient is cleared for discharge home with a plan for expedited follow-up. She will continue oral antibiotic therapy and she will return if any new or concerning issues arise.

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Introduction

Infectious complications related to cancer and cytotoxic chemotherapy remain common. A particular disease process that has the potential for significant morbidity and mortality is febrile neutropenia. Appropriate identification and management of this condition is critical given that major complications (e.g., end-organ damage, need for mechanical ventilation) occur in up to 30% of patients and the reported mortality may approach 11% [1–3]. Unfortunately, the classic signs and symptoms of infection in patients with neutropenia are often absent or muted, with fever being the only presenting symptom in many cases [4]. This makes it difficult for the treating clinician to diagnose the underlying cause and provide directed therapy against potential infectious agents. Almost universally, patients are treated for potentially serious and life-threatening bacterial infections. Many patients, however, may suffer from viral or fungal pathogens, while others may experience fever due to underlying malignancy and/or therapeutic agents. Due to this diagnostic dilemma, the ultimate disposition of these patients becomes quite challenging. Which patients can safely be discharged and which require hospitalization?

In this chapter, we will address the most recent literature and recommendations relating to the diagnosis and treatment of febrile neutropenia in the acute setting. We will discuss the current best-practice guidelines in the identification of a low-risk patient cohort, who may be safely treated in the outpatient setting. Finally, we will discuss future considerations in febrile neutropenia diagnosis and risk stratification.

Definition

Febrile neutropenia is a vitally important complication of chemotherapy. Neutrophils are an essential component of the immune response, especially against bacteria and fungi, and febrile neutropenia may be the only sign of a serious infection in an immunocompromised patient [1, 5]. Neutropenia

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is typically categorized as mild, with an absolute neutrophil count (ANC) 1000–1500 cell/μL; moderate, with an ANC 500–1000 cells/μL; and severe, with an ANC <500 cells/μL [6]. Per the American Society of Clinical Oncologic (ASCO) and Infectious Diseases Society of America (IDSA), febrile neutropenia is defined as a single oral temperature (either obtained in a healthcare setting or self-reported) of ≥38.3 °C (101°F) or a sustained temperature of ≥38.0 °C (100.4°F) for 1 h, with an ANC <500 or an ANC expected to decrease to <500 in the next 48 h [5, 7].

Pathophysiology

Many cytotoxic chemotherapy regimens work by targeting rapidly dividing cancer cells, but in the process also damage the patient's normal cells, including those that make up the immune system and mucosal linings. Not only does this leave the patient immunocompromised, but the breakdown of mucosa anywhere along the gastrointestinal tract allows for seeding of the bloodstream with endogenous flora; this is thought to cause the majority of febrile neutropenia cases [4]. Patients may also be more susceptible to infection because of the underlying cancer. Hematologic malignancies by definition have a defect in some aspect of the immune system. Solid tumors can also cause obstruction to the hepatobiliary, gastrointestinal, bronchial, and renal tracts, which can serve as a nidus for infection. Surgery and the presence of implantable venous access devices also pose a risk of infection.

Neutropenia normally occurs 5–10 days after chemotherapy [8]. Patients with solid tumors undergoing cytotoxic chemotherapy typically still have healthy bone marrow, and neutropenia generally lasts less than 7 days. In contrast, patients with hematologic malignancies undergoing chemotherapy and/or hematopoietic stem cell transplantation (HSCT) may have extended periods of neutropenia lasting more than 14 days [9, 10]. It is estimated that 5–30% of patients receiving chemotherapy for solid tumors will develop febrile neutropenia, while the rate of this complication is >80% for patients with leukemia or those undergoing HSCT 5. Other factors that increase the risk of febrile neutropenia include metastatic cancer, mucositis, chronic obstructive pulmonary disease, and advanced age [11]. The cytotoxic chemotherapies associated with the highest risk of neutropenia include anthracyclines, taxanes, platinums, ifosfamide, cyclophosphamide, etoposide, and cytarabine [11, 12].

An infectious source is identified in only 40–50% of febrile neutropenia cases, with bacteremia identified in 10–25% [7, 13]. An additional 20–25% of patients have an identifiable site of infection (e.g., pneumonia, cellulitis), but no identifiable causative organism [10]. Less than 5% of cases have a non-infectious cause of fever, such as drug fever or tumor fever; as such, this should be a diagnosis of exclusion [14]. It is suspected 80% of infections arise from endogenous flora. Interestingly, over time there have been changes in the most common identified pathogens. Historically until the 1980s, gram-negative bacilli predominated, particularly *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella* species, and *Enterobacter* species [10, 15]. Since then, gram-positive cocci have become more common, particularly *Staphylococcus epidermidis*, and, to a lesser extent, *Staphylococcus aureus*, and streptococci [16, 17]. It is suspected the cause of this transition is the increasing prevalence of implantable venous access devices, as well as the use of prophylactic fluoroquinolone antibiotics, which are primarily active against gram-negative species. More recently however, there has been a trend back toward gram-negative bacteremia, particularly multidrug-resistant organisms [18].

Fungal pathogens can also cause neutropenic fever, though they are rarely associated with the first episode [10]. The risk of fungal infection increases with the duration and severity of the neutropenia, particularly with profound neutropenia lasting more than 10–15 days [19]. Most commonly, *Candida* species were identified in central venous catheter-associated infections and gastrointestinal tract colonization, while *Aspergillus* was identified more commonly with respiratory tract infections [20]. Severely immunocompromised patients are also at risk for mucormycosis, invasive *Fusarium* infection, and new infection or reactivation of endemic fungi such as *Coccidioides*, *Histoplasma*, and *Blastomyces* [10, 20]. Other opportunistic infections should also be considered, including tuberculosis, *Pneumocystis jirovecii*, and *Mycobacterium avium complex*.

Viral infections are also a common cause of febrile neutropenia. Community-acquired respiratory viruses are of particular concern and have been documented with increasing frequency in neutropenic patients, particularly seasonal influenza, respiratory syncytial virus, parainfluenza, adenovirus, rhinoviruses, human metapneumovirus, and coronaviruses, including the novel corona virus, COVID-19 [21, 22]. Reactivation of human herpesviruses, particularly herpes simplex virus-1 and 2, and herpes zoster, is also very common, however typically only in those with hematologic malignancies and prolonged neutropenia. As a result, it is standard practice to start empiric antiviral prophylaxis on most patients with hematologic malignancies prior to the commencement of chemotherapy [7, 23].

Assessment

A patient with febrile neutropenia may present with vague nonspecific complaints [24]. Due to the muted inflammatory response in an immunocompromised patient, fever may often be the only presenting sign or symptom. The assessment of temperature can be particularly tricky and is often the turning point between discharging a patient home or starting broad-spectrum antibiotics in the hopes of not missing life-threatening illness. An oral temperature is the preferred method, though care should be taken in those with significant oral mucositis, which may also falsely elevate the temperature [25]. Rectal thermometry is not recommended in neutropenic patients due to the potential risk of mucosal injury leading to bacteremia.

A thorough history should be obtained to evaluate the risk of serious complications and help determine the potential site of infection [7]. Important factors to assess include medical comorbidities, a thorough review of systems, chemotherapeutic regimen and timing of last cycle, use of antibiotic prophylaxis or recent antibiotic treatment, and history of prior infections or colonization with multidrug-resistant organisms. A careful physical examination should be performed, with special attention to the skin, biopsy sites, catheter sites, oropharynx, lungs, abdomen, genitals and perianal area, and decubitus sites.

Patients with febrile neutropenia require a broad diagnostic workup, consisting of a complete blood cell count with differential, a complete metabolic panel with liver function tests, and an evaluation of all possible sources of infection. This includes, but is not limited to, urinalysis, urine culture, two blood cultures obtained from peripheral sites and additional blood cultures from each central venous catheter, sputum culture for respiratory symptoms, and stool sample for gastrointestinal symptoms. Consider lumbar puncture and cerebrospinal fluid (CSF) cell count, culture, and PCR testing if there is a high index of suspicion for meningitis or encephalitis. Consider fungal blood cultures, fungal serum markers, and a beta-D-glucan assay in patients with persistent neutropenic fever or a history of prior invasive fungal infection. Have a low threshold for respiratory viral testing, especially during influenza season or other viral epidemic. However, caution should be exercised when interpreting any of these tests in a neutropenic patient; the absence of typical laboratory findings does not exclude infection in the immunocompromised patient.

Patients with respiratory symptoms should have a chest radiograph, with a low threshold to proceed to chest computed tomography (CT) given the high prevalence of occult pneumonia [26]. Additional advanced imaging can be obtained according to suggestive symptoms (e.g., head, sinuses). Of particular note is CT of the abdomen/pelvis, with contrast when possible, which should be obtained for patients with any abdominal complaints, especially if there is a concern for neutropenic enterocolitis (Table 39.1).

Table 39.1 Diagnostic evaluation of febrile neutropenia

Should obtain for all patients
CBC with diff
CMP
Peripheral blood cultures × 2
Urinalysis and urine culture
Chest x-ray
Strongly consider for all patients
Viral respiratory pathogen panel
Patient-specific additional testing
Additional blood cultures from each CVC
Sputum culture
Stool culture
Fungal cultures
Beta-D-glucan
CSF cell count and culture
CT chest/abdomen/pelvis

CBC complete blood count, *CMP* complete metabolic panel, *CVC* central venous catheter, *CSF* cerebrospinal fluid

Management

Classically, the management of febrile neutropenia has included broad-spectrum antibiotics and hospital admission. This approach minimizes morbidity and mortality by providing aggressive empirical care prior to obtaining microbiological isolates. Since the 1960s, this approach has been supported by a large body of literature in the fields of oncologic, infectious diseases, and emergency medicine [27, 28]. Additionally, hospitalization was classically continued until fevers resolved and neutrophil counts recovered. Subsequent literature, however, suggested that a more nuanced, less aggressive approach may be appropriate for a subset of low-risk patients [29, 30]. This section will first cover febrile neutropenia risk stratification, followed by a discussion on empiric antibiotic therapy and disposition considerations.

Risk Stratification

The risk of severe disease among patients with febrile neutropenia depends on several factors, including the cancer type, medical comorbidities, and a variety of findings on history and physical exam. Patients with a prior history of opportunistic infections, those with anticipated prolonged neutropenia (>7 days less than 100 ANC), or those who have received more intense cytotoxic chemotherapy are known to be of higher risk. Patients with risk of prolonged neutropenia include those who have received several courses of

Table 39.2 MASCC Risk Index Score ≥21 indicates that the patient is low risk for complications

Characteristic	Weight
Burden of illness with no or mild symptoms	5
Burden of illness with moderate symptoms	3
No hypotension (systolic blood pressure >90 mm Hg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection	4
No dehydration requiring parental fluids	3
Outpatient status at onset of fever	3
Age <60 years	2

MASCC Multinational Association for Supportive Care in Cancer

Table 39.3 Clinical Index of Stable Febrile Neutropenia (CISNE) score

Characteristic	Points
ECOG PS ≥2	2
Stress-induced hyperglycemia	2
Chronic obstructive pulmonary disorder	1
Chronic cardiovascular disease	1
Mucositis National Cancer Institute grade ≥2	1
Absolute monocyte count <200 μL	1

ECOG PS Eastern Cooperative Oncologic Group Performance Scale

myelosuppressive chemotherapy, allogeneic stem cell recipients, patients with bone marrow metastases, and those who have received radiation to the pelvis or long bones [31]. Additionally, those patients who receive alemtuzumab are known to be at particular high risk. Patients with a lower baseline functional status (Eastern Cooperative Oncologic Group Performance Scale [ECOG PS] ≥2) are more likely to develop severe disease. Other indicators of high-risk febrile neutropenia include hepatic or renal insufficiency, uncontrolled or progressive cancer, grade 3–4 mucositis, or those with more life-threatening infectious sources (pneumonia, meningitis, encephalitis, etc.) [31].

One of the most widely accepted tools to aid clinicians in the risk stratification of patients with febrile neutropenia is the Multinational Association for Supportive Care in Cancer (MASCC) score. First published in 2000 by Klastersky et al., the MASCC score synthesizes of variety of clinical and historical data to produce a neutropenic fever risk score (Table 39.2) [30]. Points are assigned based on the lack of high-risk features with a score ≥21 considered as low risk and potentially appropriate for outpatient management (maximum score of 26). Of note, this score was only validated in the adult population and should not be used to risk stratify children.

A more recent risk stratification tool, the Clinical Index of Stable Febrile Neutropenia (CISNE) score, was validated in 2015 by Carmona-Bayonas et al. and specifically targets those patients with solid tumor malignancies (Table 39.3) [2]. This score utilizes similar historical risk factors as the MASCC score but eliminates symptom burden and adds certain laboratory values (absolute monocyte count, presence of hyperglycemia) as well as functional status (ECOG PS). In studies that compared the CISNE and MASCC scores, the CISNE score appeared to have a greater sensitivity in the identification of a low-risk cohort, with fewer patients misclassified as low risk [32, 33]. The most recent American Society of Clinical Oncologic (ASCO) and Infectious Diseases Society of America (IDSA) Joint guideline on the safe discharge of low-risk patients with febrile neutropenia supported the application of the CISNE score to patients with solid tumor malignancy who have received mild- to moderate-intensity chemotherapy. Studies evaluating these risk stratification tools in the ED have similarly supported utilizing the CISNE score to identify low-risk febrile neutropenia patients with solid malignancy who may be suitable for outpatient management [34].

Table 39.4 ASCO/IDSA safe discharge criteria for patients with febrile neutropenia

Residence ≤1 h or ≤30 miles (48 km) from clinic or hospital
Patient's primary care physician or oncologist agrees to outpatient management
Able to comply with logistic requirements, including frequent clinic visits
Family member or caregiver at home 24 h/d
Access to a telephone and transportation 24 h/d
No history of noncompliance with treatment protocols
The following additional measures are recommended:
Frequent evaluation for at least 3 days in clinic or at home
Daily or frequent telephone contact to verify (by home thermometry) that fever resolves
Monitoring of ANC and platelet count for myeloid reconstitution
Frequent return visits to clinic

With regard to febrile neutropenia risk stratification in the pediatric population, there is no universally accepted risk stratification tool. To date, there have been at least 27 attempts to derive a validated score to appropriately categorize pediatric patients as low or high risk; however, none of these scores have achieved adequate sensitivity or specificity [35–38].

Finally, there are several social considerations that must be addressed prior to safely discharging low-risk febrile neutropenic patients. The ASCO/IDSA safe-discharge criteria are listed in Table 39.4 [1].

Antibiotic Therapy

It is recommended that all patients presenting with febrile neutropenia rapidly receive broad-spectrum empiric antibiotics. The joint ASCO/IDSA guidelines state that all patients with febrile neutropenia should receive appropriate antibiotic therapy within 1 h of triage [1]. Perron et al. demon-

strated that early antibiotics significantly decreased hospital length of stay for patients with febrile neutropenia who received early antibiotics. Rosa et al. found there to be a decrease in 28-day mortality for patients who received early antibiotic therapy (within 30 min), with an increase in 28-day mortality by 18% for each hour that antibiotics were delayed [39, 40]. A more recent, well-powered study by Daniels et al., however, demonstrated that only more significant delays in antibiotic administration (>3 h) were associated with increased length of stay and 30-day mortality [41].

Several factors must be considered when choosing the initial antibiotic course including previous culture data, the presence of indwelling catheters, site of infection, organ dysfunction, drug allergy, previous antibiotic therapy, and local antibiograms/sensitivities. Choosing the correct empiric antibiotic is likely the most important modifiable factor affecting the morbidity and mortality of a patient with febrile neutropenia [42, 43]. Previous literature has demonstrated that inappropriate empiric antibiotics may lead to a significant increase in mortality, especially in cases of *Pseudomonas aeruginosa* [44]. Consensus guidelines have been published by the National Comprehensive Cancer Network (NCCN) to guide clinicians in the initial selection of antibiotics for patients with febrile neutropenia (Table 39.5) [31]. Note, however, that one should synthesize all available information (previous cultures, specific risk factors, etc.) before choosing an initial antibiotic.

In an era of increasing antibiotic resistance, there are emerging data that suggest alternating first-line therapies may be beneficial to decrease antibiotic resistance. This strategy has been shown to be effective in increasing antibiotic heterogeneity without worsening outcomes [45, 46]. A recent study among pediatric patients with febrile neutropenia specifically demonstrated a significant decrease in extended-spectrum β-lactamase producers in blood and stool cultures after implementation of antibiotic cycling over a 3-year period [47].

Table 39.5 Typical empiric antibiotic therapy for patients with febrile neutropenia

Inpatient therapy (intravenous)	Outpatient therapy (low risk) (per os)
Cefepime	Ciprofloxacin[a] + amoxicillin/clavulanate
Imipenem/cilastatin	Moxifloxacin[a]
Meropenem	Levofloxacin[a]
Piperacillin/tazobactam	
Ceftazidime[b]	
Vancomycin[c]	

[a]Patients previously on fluoroquinolone prophylactic therapy are not candidates for oral antibiotic therapy

[b]Weak gram-positive coverage may limit utility

[c]Consider vancomycin in patients who have a history of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization, clinical instability, soft tissue infection with high risk of MRSA, or indwelling intravenous catheters

If a patient is risk-stratified into a low-risk cohort after utilizing a validated scoring method, it is appropriate to consider treatment with oral antibiotics. First-line oral therapy typically consists of ciprofloxacin and amoxicillin/clavulanate. Alternative monotherapies with either moxifloxacin or levofloxacin are acceptable. Of note, if a patient was on prophylactic therapy with a fluoroquinolone prior to presentation, these oral regiments should not be utilized. Several studies have demonstrated non-inferiority of oral versus intravenous antibiotics in low-risk patients with febrile neutropenia [48–50]. Given increasing reports of adverse reactions to fluoroquinolone therapy (tendinopathies, CNS complications, etc.), it is important to discuss these potential risks with patients discharged on these oral agents [51, 52]. It is recommended that patients who are identified as potential candidates for home therapy are observed for a period of time in the ED prior to discharge (4–12 h).

Antifungal Therapy

Empiric antifungal therapy is not typically recommended in the acute setting, unless the patient has known invasive fungal disease or has physical exam findings suggestive of invasive fungal disease (i.e., mucormycosis). In general, antifungal therapy is initiated only after 4 or more days (average 7–10 days) of persistent fevers despite broad-spectrum antibiotic therapy [53, 54]. Those with the highest risk of mold infections (neutropenia >10 days, allogenic stem cell recipient, prolonged steroid use) should receive early antifungal coverage (4 days of persistent fever), unless they are already on prophylactic antifungal medications [55].

Antiviral Therapy

Similar to antifungal therapy, antiviral therapy is not typically recommended in the acute setting, unless there is clear indication of a viral infection prompting treatment (i.e., HSV, VZV). It is prudent to assess for common viral upper respiratory infections with a respiratory viral polymerase chain reaction (PCR) swab. Additionally, assessing and treating for influenza may be indicated, especially if a patient presents with the appropriate constellation of symptoms [7].

Granulocyte Colony-Stimulating Factor (GCSF)

Although there is a role for the use of GCSF to prevent febrile neutropenia in patients receiving myelosuppressive therapy, the use of GCSF in patients with established febrile neutropenia has been controversial. Overall, the medication appears to have a negligible effect on patient-centered out-

comes [56]. Specifically, GCSF given during febrile neutropenia does not improve overall patient mortality [57]. Conversely, patients receiving GCSF typically have a shorter duration of neutropenia, faster recovery from fever, and shorter duration of antibiotic use.

Future Considerations

Biomarkers

A significant proportion of patients with febrile neutropenia have little or no symptoms to assist clinicians in making a definitive diagnosis. Although some patients may have non-infectious causes of fever (tumor fever, drug fever) or minor viral infections, there is a subset of febrile neutropenic patients who appear clinically well, despite bacteremia. Unfortunately, blood cultures are classically insensitive and are prone to false positives due to contamination with skin flora. This has led researchers to explore several biomarkers as potential risk stratifications tools to predict poor outcomes in patients with febrile neutropenia.

Procalcitonin (PCT) has emerged as a valuable biomarker to help clinicians differentiate between bacterial illness and alternative causes of inflammation/infection. Unfortunately, previous literature has demonstrated a high variability in PCT levels among patients with febrile neutropenia, and there have been reports of bacteremia in patients with low procalcitonin levels [58, 59]. Serial PCT levels may provide improved discriminatory power [60].

CRP has also been proposed as a possible biomarker to aide in risk stratification. Overall, CRP may have a slightly higher sensitivity than procalcitonin (using a cutoff of >20 mg/L for CRP and >0.2 ng/ml for PCT). However, this sensitivity (0.82, 95% CI) is still too low to safely utilize CRP alone to risk stratify patients. Additionally, PCT appeared to be more discriminatory than CRP at time of disposition.

Interleukin-6 (IL-6) and interleukin-8 (IL-8) may also provide some insight into the risk of severe febrile neutropenia. Both IL-6 and IL-8 appear to have better predictive value than CRP for high-risk febrile neutropenia, with one study reporting that low IL-8 levels predicted patients at low risk for bacteremia with a sensitivity of 0.9 and a negative predictive value of 0.98 [61, 62].

Overall, biomarkers may prove to be very important in differentiating high- vs low-risk febrile neutropenia. Currently, however, the body of literature is lacking, and more evidence is needed before utilizing a single biomarker (or a combination of biomarkers) to definitely risk stratify patients.

Conclusion

Febrile neutropenia is a common complication of cytotoxic chemotherapy, and despite decades of study, it continues to present challenges for acute care providers. It is imperative to initiate a broad workup for these patients and provide rapid, broad-spectrum antibiotic therapy. For clinically stable patients, it is appropriate to apply validated risk stratification tools to identify a low-risk cohort appropriate for discharge. For patients qualifying for outpatient management, one must assure that the proper outpatient structure is in place prior to discharge. Treatment with antibiotics should cover both typical and atypical organisms and should account for previous cultures as well as the bacterial sensitivities of a particular hospital or region. As biomarkers for disease severity are developed and validated, we may more objectively identify patients at higher or lower risk for severe disease.

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Neutropenic Enterocolitis

40

Steven McGaughey and Robert L. Cloutier

Case Study

A 70-year-old man with acute myeloid leukemia on daunorubicin and cytarabine for induction therapy presents to the emergency department (ED) after suddenly developing fever, diffuse abdominal pain, and diarrhea. On review of his chart, it is noted that he has been neutropenic (absolute neutrophil count (ANC) = 350/dL) since 9 days prior to presentation. Today, vitals are notable for a respiratory rate of 19 breaths per minute, sinus tachycardia of 120 beats/min, and blood pressure of 105/60 mmHg. On exam, he has right lower quadrant abdominal pain with associated involuntary guarding. Laboratory evaluation reveals a white blood cell count of 1200 cells/μL (ANC = 100/dL), a hematocrit of 23%, and 40,000 platelets/μL. Computed tomography (CT) scan of the abdomen and pelvis shows thickening of the colonic wall with diffuse pericolic edema and pneumatosis. Since the differential diagnosis includes a strong suggestion of neutropenic enterocolitis, the hematology and surgical teams are promptly consulted. The patient is admitted and started on intravenous fluids, ceftazidime and metronidazole, as well as granulocyte colony-stimulating factor (G-CSF). The next day, the patient becomes hemodynamically unstable and is transferred to the intensive care unit where he remains on broad-spectrum antibiotics with close monitoring. On hospital day 5, he shows clinical improvement. Blood cultures remain no growth, and stool studies are negative for Clostridium difficile (C. difficile) or other enteropathogenic organisms. With continued conservative management, the patient had full resolution of symptoms following 14 days of treatment.

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Introduction

Neutropenic enterocolitis (NE) is a poorly understood and life-threatening complication of severe neutropenia [1]. While it is most often seen in patients with hematologic malignancies, it can be seen in a wide range of disease processes. NE was first reported as a complication of treatment of childhood leukemias and remains most common in pediatric patients [2]. However, NE is increasingly documented in adults as well, especially in those patients on intensive chemotherapies for hematologic malignancies. Incidence is variable with rates ranging from 0.8% to 26% with a pooled incidence rate of 5.3% [3–5]. Clinical manifestations of NE include fever, abdominal pain or distension, diarrhea, and intestinal bleeding. There are no pathognomonic manifestations or strict diagnostic criteria; thus, a high level of clinical acumen is required to make a prompt diagnosis and start appropriate treatment [1].

NE most commonly occurs 2–3 weeks after chemotherapy is initiated. At this time, a combination of impaired mucosal defense and intestinal injury leaves the bowel susceptible to bacterial invasion with possible progression to perforation [1, 6, 7]. If untreated, these patients can quickly progress to sepsis syndrome with resultant multisystem organ failure. Early reports of NE in the 1960s were almost uniformly fatal. Over the subsequent decades, outcomes have improved; however, morbidity and mortality remain high at between 50% and 100% [8–12].

With the advent of new chemotherapies, more patients than ever are at risk for developing NE, including those with both hematologic malignancies and solid tumors [1, 13]. Emergency physicians and other frontline medical professionals are critical in rapidly identifying and treating neutropenic patients. Given the high morbidity of NE, it is essential that these clinicians have familiarity with this disease process to allow them to more promptly detect and treat these patients appropriately.

This chapter will discuss the background, clinical presentation, diagnostic criteria, risk factors, pathophysiology,

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workup, and management of NE. We note that the nomenclature of NE is heterogeneous; typhlitis, ileocecitis, and cecitis have all been used synonymously in the literature to describe NE. For clarity, we have chosen to use the term NE exclusively in this chapter. This should not be confused with necrotizing enterocolitis or NEC, a separate and unrelated neonatal disease.

Background and State of the Evidence

The first description of NE dates back at to 1933, when Cooke noted submucosal hemorrhage and appendiceal perforation in children with leukemia [2]. More contemporary reports date to 1962, with a case series by Amromin and Salomon [14]. As noted in a review by Cunningham, these patients almost uniformly experienced abdominal pain, distension, leukopenia, and intestinal necrosis with histologic evidence of bacterial invasion of the mucosal and submucosal bowel wall [8]. These patients characteristically developed necrotizing enteric lesions shortly after intensive chemotherapy. These lesions developed regardless of whether the patient responded to chemotherapy. In fact, most patients with NE actually experience excellent therapeutic response prior to developing NE. Unfortunately, the subsequent clinical course in patients diagnosed with NE in the 1960s was marked by hemodynamic collapse and death.

Since then, there have been numerous reports of NE across a spectrum of patients, both with and without cancer. However, the current literature suffers from many limitations. First, these articles have mainly been restricted to case reports and series. A recent review by Gorschlüter noted that, of the 145 papers on neutropenic enterocolitis, there were no clinical trials or case-control studies. The few remaining prospective studies have significant limitations and meet only level 3b evidence according to the Oxford Center for Evidence-Based Medicine [5]. Second, there are no unified diagnostic criteria for NE. As a result, the overall grade of the evidence in neutropenic enterocolitis is low. An editorial by Gorbach summed up the challenges of understanding NE: "the diversity of the pathology is matched by the difficulty in establishing the diagnosis on the basis of only clinical findings" [9]. Despite these challenges, clinicians have made progress in early recognition and treatment of NE, leading to meaningful improvements in patient outcomes [1].

Clinical Presentation

Most patients with NE will present with a combination of diffuse crampy abdominal pain, vomiting, abdominal distension, and diarrhea [1, 10, 15, 16]. The location of abdominal pain is most often diffuse with or without rebound tenderness. Some patients do have localized abdominal pain when NE affects a specific segment of bowel. For example, patients frequently experience right lower quadrant pain which may be due to distension of, and limited blood supply to, the cecum [10, 15]. Patients can have hematochezia or melanotic stools; however, the frequency of these presentations is varied [7, 11, 17, 18]. Peritoneal signs, such as abdominal rebound, guarding, or abdominal distension, may be present if patients develop intestinal perforation. While fever is common, it may be absent in severely immunocompromised patients [10, 15, 16, 19, 20].

Table 40.1 Common signs and symptoms of neutropenic enterocolitis

Vague diffuse crampy abdominal pain
With or without peritoneal signs including rebound and/or guarding
If localizes: more commonly to the right lower quadrant
Abdominal distension
Diarrhea
Fever
Melanotic stools or hematochezia

Overall, the clinical presentation of NE is variable with significant overlap between NE and many other abdominal pathologies representing infectious, chemotherapeutic, and malignancy-induced as well as primary and surgical conditions or causes. The differential diagnosis includes infections, such as *C. difficile* colitis, and chemotherapy-induced conditions, such as mucositis, mycophenolate injury, as well as graft-versus-host disease (GVHD); malignancy-induced conditions, such as recurrent lymphoma and leukemic infiltration; and, lastly, surgical conditions, such as appendicitis or intussusception [1, 7, 12, 21]. Clinically, it is difficult to differentiate between these conditions; thus, prompt imaging is crucial to diagnose NE.

Common presenting signs and symptoms are summarized in Table 40.1.

Diagnostic Criteria

There are currently no universal diagnostic criteria for NE. This is largely due to the vast heterogeneity in pathological, radiographic, and clinical diagnostic criteria across the literature. In 2005, Gorschlüter published a systematic review of NE literature and proposed the diagnostic criteria listed in Table 40.2 [5], which include clinical signs, such as fever and abdominal pain, in combination with imaging findings. While these criteria have been generally accepted, some suggest refining the criteria to include the presence of neutropenia (ANC < 500 × 106 cells/L) and to rule out alternative conditions, such as GVHD, *C. difficile* colitis, and appendicitis [1]. Still others debate including fever as a

Table 40.2 Suggested diagnostic criteria for neutropenic enterocolitis

Presence of fever (axillary temperature >38.0 °C or rectal temperature >38.5 °C)
Abdominal pain (at least degree 3 determined by the patient using a visual analogous scale pain score ranging from degree 1 to 10)
Demonstration of the bowel wall thickening of more than 4 mm (transversal scan) over more than 30 mm (longitudinal scan) in any segment by US or CT

From Gorschlüter et al. [5], with permission John Wiley
US ultrasound, *CT* computed tomography

criteria given how poorly fever correlates with the ultimate diagnosis of NE [22]. Regardless, most authors broadly agree that a combination of clinical signs and symptoms with bowel wall thickening (BWT) on imaging is most appropriate to ultimately diagnose NE.

NE remains a difficult diagnosis for frontline clinicians, including emergency physicians. Neutropenic patients on chemotherapy are at high risk to develop many possible complications. Consequently, clinicians must perform a thoughtful and thorough evaluation and have a high index of suspicion for NE in neutropenic patients presenting with abdominal pain.

Risk Factors

There are several risk factors for developing NE. Numerous chemotherapeutic agents are strongly associated with NE. Cyclophosphamide, 5-fluorouracil, and its prodrug capecitabine, ifosfamide, cisplatin, carboplatin, gemcitabine, cytosine arabinoside, vincristine, doxorubicin, idarubicin, leucovorin, and daunorubicin are all associated with NE [10, 13, 15, 23–25]. Additionally, taxanes (docetaxel, paclitaxel) and vinorelbine, which are used for solid tumors, have been implicated in recent reports [1].

Beyond the chemotherapeutic agents themselves, the risk of a patient developing NE changes depending on the timing of chemotherapy and the resultant duration of neutropenia. The average time between chemotherapy and development of NE ranges from 12 to 17 days. It is during this time frame when cytotoxic chemotherapy causes maximal injury of the mucosal barrier and makes NE possible [26–28]. Some patients will develop NE later in their chemotherapeutic course; however, most NE patients will have neutropenia 2–9 days before developing symptoms [7, 11, 15]. While later onset is less common, this specific population is at an increased risk of death [11]. Other factors associated with increased mortality include older age, more severe and prolonged neutropenia, and concomitant systemic infections [11].

Lastly, there is an association between the type of malignancy and NE. Early cases of NE were found almost exclusively in pediatric leukemias. Today, while the majority of cases of NE are still found in patients with leukemia and lymphoma, a growing number of NE cases are found in patients with solid tumors including breast, lung, colorectal, and ovarian cancer [10, 13, 23, 24]. Overall, patients with hematologic malignancies who develop NE portend a worse overall survival. This may be linked to the longer duration and more profound neutropenia seen with these malignancies and their associated treatments [11].

While most NE is associated with specific chemotherapies, there are a small number of reported cases in patients prior to initiation of treatment [17, 29, 30]. Additionally, there are rare cases of non-oncologic conditions leading to NE. A single trauma patient developed NE in the setting of reversible neutropenia secondary to nafcillin therapy for osteomyelitis [19]. Other cases have been reported in the setting of aplastic anemia, cyclic neutropenia, acquired immunodeficiency syndrome, and immune-suppression for bone marrow or renal transplantation [19, 20]. Overall, any condition which causes prolonged neutropenia places patients at risk for developing NE.

Pathophysiology

The pathophysiology of NE is multifactorial and incompletely understood. The primary effects of neutropenia decrease the immunologic response against intestinal invasion, making the patient more susceptible to infection. Secondly, the intestinal wall is damaged through a number of mechanisms: direct destruction due to chemotherapy and/or radiation, leukemic or lymphomatous infiltrates, or intramural hemorrhage secondary to severe thrombocytopenia. This compromised mucosa ultimately allows translocation of normal gut microbial flora [1, 6, 7, 11, 31]. Innate immunity of the submucosal tissue and proinflammatory mediators leads to a cascade of events culminating in epithelial cell apoptosis and mucosal permeability. Visualized bowel is thickened and edematous with hemorrhage and ulceration [1]. As noted previously, the cecum is particularly susceptible to injury secondary to its more limited blood supply. However, while NE most commonly affects the cecum, this condition may affect any portion of the intestinal tract.

The combination of mucosal injury and neutropenia places patients at high risk of developing bacteremia from gut flora, including *Enterococcus*, *Klebsiella*, and coagulase-negative *Staphylococcus* [11, 12]. In addition, *C. difficile* is commonly seen in NE, but it is generally not thought to be pathogenic as there is no mortality difference in patients with or without this pathogen [32]. Invasive fungal infections, mostly commonly by *Candida*, occur in approximately 5% of cases [33]. Bacteremia is more common, with positive blood cultures found in 28–80% of definite cases of

NE [7, 15, 34]. Overall, while the most common single isolate from blood cultures are aerobic gram-negative bacilli, most cultures show polymicrobial infections [7, 11, 35]. There is no data to suggest that a specific organism or combination of pathogens is associated with NE.

Pediatric Considerations

Considerations in the pediatric population closely mirror those of adults. Hematopoietic malignancies such as acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML) are most commonly associated with NE in the pediatric population [36, 37]. The incidence has been reported to be higher in pediatric patients, varying between 2.6% and 16.2%, which may reflect the highly aggressive malignancies and associated intensive chemotherapy regimens used for treatment [36–39]. A study by McCarville characterizing NE in pediatric patients noted that, similar to adults, diagnosing NE in children based on symptoms alone, is challenging [37]. The clinical presentation of NE in pediatric patients is similar to adults and includes abdominal tenderness, fever, diarrhea, and nausea. However, in 9–16% of cases, typical signs and symptoms, including abdominal pain, fever, and neutropenia, were absent [37]. Overall age, race, and gender are poorly associated with risk of NE; however, patients older than 16 years had an increased odds ratio of NE and had poorer response to therapy than younger patients. Medications and chemotherapeutic agents associated with pediatric NE include GCS-F, topotecan, atovaquone, PEG-L-asparaginase, idarubicin, cytosine arabinoside, hydrocortisone, methotrexate, and carboplatin. Additionally, treatment with cytarabine and presenting with abdominal distention are poor prognostic factors, which are associated with increased mortality [36].

Workup

Initial workup for NE requires ruling out other common conditions, including *C. difficile* colitis, GVHD, and other abdominal pathology, while meaningfully addressing the broader threats posed by potential neutropenia. Thus, initial laboratory testing, including complete blood count, coagulation studies, chemistry panel, and *C. difficile* toxin or polymerase chain reaction (PCR) assay, is recommended. While no laboratory tests will confirm the diagnosis of NE, presence of neutropenia in the absence of other abdominal pathologies strongly suggests a patient is at risk for NE. In these patients, additional imaging is critical in making the correct diagnosis and starting appropriate treatment.

The Role of Diagnostic Imaging: CT and Ultrasound

Because the clinical presentation is nonspecific, imaging is essential in the diagnosis of NE. Computed tomography (CT) and ultrasonography (US) are the most common modalities for diagnosing NE. Conversely, plain radiographs are of limited utility; while positive findings, such as paucity of air in the cecum with associated pneumatosis, can be helpful, most x-rays are nonspecific or normal.

Many clinicians favor CT to evaluate for NE. CT provides a more detailed view of bowel integrity and better characterizes surrounding abdominal inflammation and bowel wall thickening (BWT) (Fig. 40.1) [12, 16, 27, 40, 41]. In addition, CT provides better visualization of other radiographic features of abdominal pathology, including pneumatosis and nodularity. This becomes clinically important when trying to differentiate between NE and other mimics. A retrospective

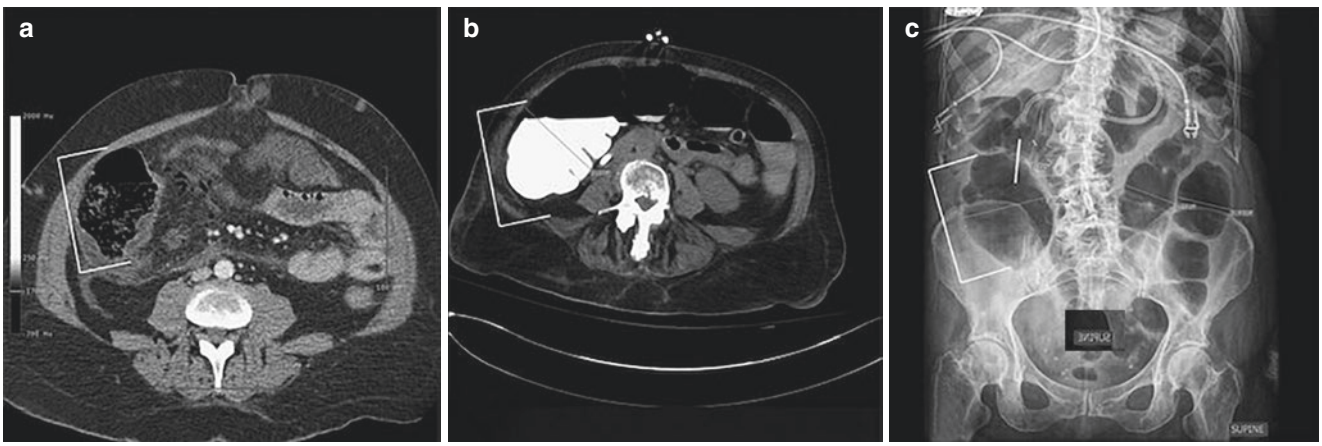

Fig. 40.1 NE imaging findings. (**a**, **b**) Computed tomography images from two different patients with NE; both show cecal wall thickening and dilation (*brackets*). (**c**) Colonic dilatation on an abdominal radiograph; findings are most prominent in the cecum (*bracket*). (From Sachak et al. [12], with permission Wolters Kluwer)

study characterized the CT features of neutropenic patients with radiographic bowel abnormalities—noting specific patterns of BWT, pneumatosis, and nodularity on CT—useful in distinguishing NE from other pathologies, including GVHD, cytomegalovirus colitis, and *C. difficile* colitis [41]. NE was also best characterized by its predilection for the right colon and cecum, with occasional involvement of the small bowel. Lastly, NE exhibited the greatest degree of pneumatosis and mesenteric stranding when compared with GVHD or *C. difficile* colitis [41].

While CT provides highly detailed images, ultrasound can be deployed more quickly and avoids radiation. In an emergent setting, ultrasound-derived BWT measurements can be used to help support the diagnosis of NE or rule out other diagnoses. Measurement criteria for BWT vary due to differences in the sensitivity of sonographic machines and the small number of published studies. Nonetheless, ≥3–5 mm (outer wall to luminal surface) has often been defined as abnormal in pediatric and adult patients [10, 27, 36–38, 40, 42, 43]. Though most authors would agree that BWT of greater than 5 mm is abnormal, the prognostic significance of BWT remains unclear. A few studies, however, report that measurements of greater than 10 mm portend a poor outcome [15, 16, 27]. US is a particularly useful and radiation-free option in the pediatric population. In addition to more well-known signs, a unique finding in the pediatric population, pneumatosis intestinalis with portal venous gas, can be suggestive of pan-intestinal involvement [25].

US may also be useful as an efficient and inexpensive screening tool to initiate antibiotic therapy in the appropriate patient [44]. In a recent study, the authors used US to screen all hospitalized neutropenic patients with fever and abdominal pain and/or diarrhea to evaluate for signs of BWT. If present, they promptly started patients on antifungal agents, antibiotics, and granulocyte colony-stimulating factor. Their mortality of post-chemotherapy patients drastically reduced from 45% pre-intervention to 0% afterward, and mean diagnosis time after fever decreased from 9 days to 3 days [45].

For the emergency clinician, the most appropriate imaging modality will depend upon the hemodynamic stability of the patient. If a patient is safe to transport, he or she will benefit from a CT as this will provide more diagnostic information and help to differentiate from other serious complications of chemotherapy. However, in patients who are hemodynamically unstable, US is a powerful screening tool to evaluate for BWT at the bedside. For any patient who is critically ill, the emergency clinician should request emergent surgical consultation for possible operative resection of necrotic bowel.

Treatment

Medical Versus Surgical

There is no clear consensus on the most appropriate management of NE. Most patients will require supportive measures, including bowel rest, parenteral nutrition, and intravenous (IV) fluid support. Clinicians should also evaluate for and correct severe thrombocytopenia and coagulopathies [1]. In addition, we recommend the prudent advice by Gorschlüter: "to follow a pragmatic strategy analogous to neutropenic [fever of unknown origin], which is always treated as an infectious disease even if sometimes non-infectious causes are present" [5]. Unfortunately, there are no unified recommendations on the most appropriate antibiotics for NE patients [42, 46–49]. We recommend selecting antibiotics that cover a broad spectrum of gram-positive and gram-negative organisms as well as *Pseudomonas* and *C. difficile*. Monotherapies, such as piperacillin-tazobactam or imipenem-cilastatin, are reasonable initial choices. Duo therapies, combining another beta-lactam antipseudomonal agent with an aminoglycoside or, alternatively, cefepime or ceftazidime coupled with metronidazole, are also acceptable. Anaerobic coverage is important primarily when using a cephalosporin monotherapy [5]. Recommended doses for adults and children are summarized in Table 40.3 [51]. In

Table 40.3 Antibiotics for empiric treatment of adult and pediatric neutropenic enterocolitis

Antibiotics for empiric treatment	Dosages
In adult neutropenic enterocolitis	
Monotherapy	
Piperacillin-tazobactam	3.375 g IV Q6 h
Imipenem-cilastatin	500 mg IV Q6 h or 1 g IV Q6–8 h
Duo therapy	
Ceftazidime	1 g IV Q8–12 h ***or***
Cefepime	2 g IV Q8 h ***plus***
Metronidazole	1 g IV Q6 h
In pediatric (1–12 y of age) neutropenic enterocolitis	
Monotherapy	
Piperacillin-tazobactam	(>9 mo and <40 kg) 300 mg/kg/d IV divided Q8 h
Imipenem-cilastatin	(>3 mo) 60–100 mg/kg/d IV divided Q6 h, max 2–4 g/d
Duo therapy	
Ceftazidime	90–150 mg/kg/d IV divided Q8 h max 6 g/d ***or***
Cefepime	50 mg/kg IV Q8 h, max 2 g/dose ***plus***
Metronidazole	30 mg/kg/d IV divided Q6 h max 4 g/d

From Cloutier [50], with permission Elsevier
IV intravenous, *Q* every

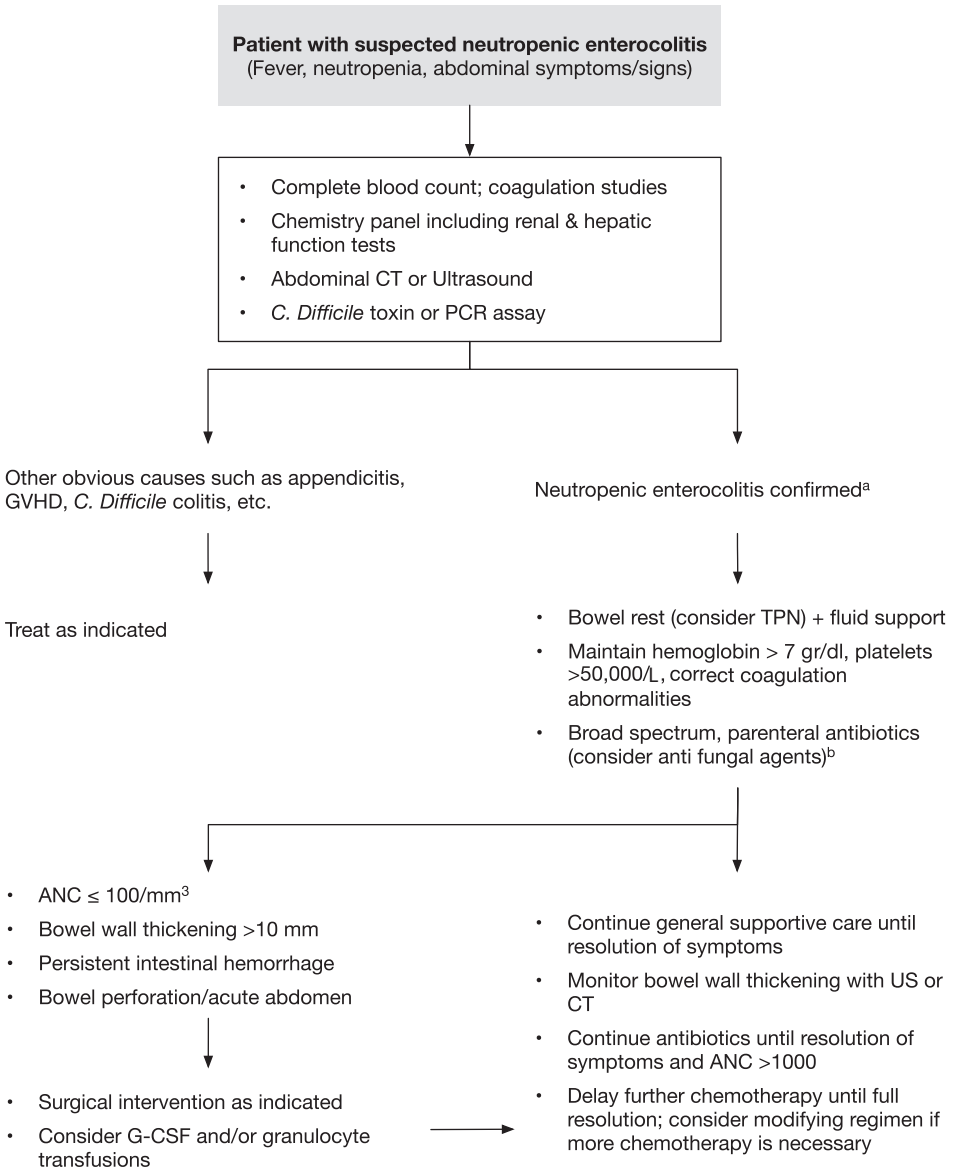

Fig. 40.2 Suggested algorithm for the evaluation and treatment of patients with suspected neutropenic enterocolitis. See Table 40.1 and text for details. ANC absolute neutrophil count, CT computerized tomography, G-CSF granulocyte colony-stimulating factor, GVHD graft-versus-host disease, PCR polymerase chain reaction, tpn total parenteral nutrition, US ultrasound. (Adapted from Nesher and Rolston, with permission Oxford University Press and the Infectious Diseases Society of America [1]). [a] see Table 40.2 for diagnostic criteria

their invited review, Nesher discourages empiric use of antifungal medications as the frequency of invasive fungemia is only 5%. They further summarized their workup and treatment algorithm which is outlined in Fig. 40.2 [1, 33].

Surgical Intervention

Historically, autopsies of patients with NE showed high rates of transmural bowel necrosis and perforation [15]. Based on this, surgical intervention with bowel resection became first-line therapy, and early studies showed this reduced overall mortality. However, the clinical presentation of NE is heterogeneous, and experts today disagree on the necessity of early surgical intervention [5, 16, 51]. More recently, as clinicians gain more experience with NE, a greater proportion of patients have been successfully managed medically with broad-spectrum antibiotic therapy [5, 15, 16]. Now, surgery is typically reserved for more severe cases, as summarized in Table 40.4; however, there is still wide variation between institutions [1, 11, 12, 49, 52]. If a patient does require non-emergent surgical management, a recent review by Badgwell

Table 40.4 Criteria for surgical intervention

Persistent gastrointestinal bleeding despite correction of coagulopathies, thrombocytopenia, and neutropenia
Intraperitoneal free air
Deterioration despite sufficient medical management, suggesting sepsis
Development of other surgical indications

suggests delaying surgery until neutropenia resolves as this lowers the overall mortality rate [22]. Overall, these recommendations are based on small case series studies; larger prospective studies are required to provide more definitive recommendations on medical versus surgical management.

If the emergency clinician suspects NE in a patient, he or she should organize critical care resources and consult surgery services early. Patients with NE are medically tenuous and have high potential to decompensate and require operative intervention.

Additional Therapy

Recombinant granulocyte colony-stimulating factor (G-CSF) has recently gained more widespread use to hasten bowel healing. In theory, G-CSF causes more rapid recovery of neutropenia which would therefore improve clinical outcomes [5, 10]. However, the data on G-CSF remains mixed. A recent large cohort study by Abu-Sbeih found that while G-CSF shortens the median time of neutropenia, it does not alter frequency of NE-related complications or mortality rates [11]. The American Society of Clinical Oncologic Clinical Practice Guidelines only recommend using a combination of antibiotics and empiric G-CSF in febrile neutropenic patients with high-risk factors including expected prolonged (>10 days) and profound (<0.1 × 109/L) neutropenia, age > 65 years, sepsis syndrome, or hospitalization at the time of fever development [53].

Despite recent gains in outcomes, morbidity and mortality remain high for NE. Treatment for a patient with NE is the same as that for other patients at risk for acute sepsis and hemodynamic collapse. An appropriate initial assessment should include venous access to support aggressive fluid support in addition to broad-spectrum antibiotics. Central venous access and an arterial line may be necessary for goal-directed therapy for sepsis. Lastly, clinicians should remain vigilant and monitor carefully for surgical indications, such as signs of an acute abdomen or hemodynamic compromise.

Summary

NE is a relatively rare but potentially devastating disease most often seen in neutropenic patients after chemotherapy. It is critical that emergency clinicians promptly identify and triage at-risk patients. Early recognition and intervention are essential to minimize morbidity and mortality in patients with NE. NE should be suspected in any neutropenic patient with abdominal pain. Patients who recently received chemotherapy are at particularly high risk. We recommend laboratory testing, including complete blood count to evaluate for neutropenia and thrombocytopenia, coagulation studies to evaluate for reversible coagulopathies, chemistry panel, and *C. difficile* toxin or PCR assay. In addition, we recommend rapid abdominal imaging. In a stable patient, CT can provide highly detailed information on bowel wall thickening which can help to differentiate between NE and other mimics. However, in the unstable patient, ultrasound may be appropriate as a fast, effective means to evaluate the bowel wall. Treatment includes bowel rest, parenteral nutrition, IV fluids, and correction of severe thrombocytopenia and coagulopathies. Broad-spectrum antibiotics with adequate coverage for intra-abdominal pathogens should be utilized. G-CSF may be beneficial in high-risk patients. Surgery services should be consulted early as NE patients can deteriorate rapidly.

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Sickle Cell Disease

41

Harsh P. Sule, Novneet N. Sahu, and Bernard L. Lopez

Case Study

A 25-year-old female with history of sickle cell disease (SCD) presents to the emergency department reporting 10/10 dull, aching pain in her back and hips. She has been taking her home regimen of morphine around the clock without relief. She took her last dose of medication just prior to arrival. She states that this is typical of prior episodes where she has needed care in the emergency department. Her vital signs are temperature of 37.2 °C, heart rate of 80 beats per minute, blood pressure of 112/72, and oxygen saturation of 99% on room air. She has a normal exam, and you do not suspect dehydration, organ failure, or neurological complications. Her old records are reviewed, and she has been previously given higher doses of morphine in the emergency department with relief. You suspect an acute painful episode associated with vaso-occlusive crisis and provide her repeat doses of pain medication. Her symptoms improve after the third dose of pain medication and she feels well. You discharge her home to continue her outpatient regimen and she will follow up with her hematologist.

Introduction

Emergency physicians (EPs) practicing in North America must be familiar with SCD and its complications. SCD is the most common inherited blood disorder in the United States [1]: 1 in 13 African American newborns has sickle cell trait, while 1 in 365 African Americans has the disease [2]. In SCD, hemoglobin molecules have a propensity to aggregate into rigid polymers, particularly under conditions of low oxygen tension, resulting in the characteristic sickle-shaped erythrocytes that cause vaso-occlusion and ischemia. The clinical hallmark of SCD is episodes of acute pain, and this is by far the most common reason for emergency department (ED) visits and inpatient admissions by SCD patients [3–6]. In addition to managing these acute pain episodes, the EP must be alert to other manifestations, complications, and comorbidities of the disease, some of which carry significant risk for morbidity and mortality.

This chapter describes the clinical presentations and management of SCD in the ED while delving into key decisions and current controversies.

Pathophysiology

SCD was first described in the Western medical literature by James B. Herrick in 1910 [7]. In 1949 James V. Neel described the pattern of inheritance, with individuals who were heterozygous for the responsible gene having sickle cell trait (SCT) and homozygous individuals having SCD [8]. SCD was the first human anemia defined at the amino acid level [9].

Human hemoglobin (Hb) molecules are typically tetramers comprising four subunit proteins (two α and two β subunits) [10]. The exact composition of the peptide chains determines the specific shape into which the molecule can fold. Hemoglobin S (HbS) is the result of a glutamic acid to valine substitution at the β6 amino acid position [11, 12]. The result is polymerization due to a hydrophobic interaction between the altered, deoxygenated molecule and other hemoglobin molecules [11]. As a consequence, there are a change in the shape and reduction in the critical ability of erythrocytes to deform [11, 12]. While initially thought that the ensuing change in flow characteristics and erythrocyte aggregation alone caused vaso-occlusion, the root cause is multi-factorial. Initial endothelial activation with increased adhesion of erythrocytes and leukocytes is followed by

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formation of heterocellular aggregates that then physically result in occlusion and local hypoxia [11]. This triggers a vicious cycle of increased HbS formation due to hypoxia, presence of inflammatory mediators, free radicals, and reperfusion injury. Hemoglobin also binds nitric oxide (NO), a potent vasodilator, and releases it with oxygen [10]. Ineffective binding and release of NO along with hemolysis and erythrocyte lysis further reduce NO production and result in persistent tissue hypoxia [10, 11, 13]. Finally, erythrocytes are more likely to sickle and become rigid the more dehydrated they get. This is in large part due to changes in cation homeostasis – specifically, increased potassium and water efflux mediated by potassium-chloride co-transport and Gardos channels (Ca^{++}-dependent K^+ channel) [11, 14]. Figure 41.1 [12] displays the pathophysiology of sickle cell disease.

Sickle cell disease is commonly represented by the primary HbSS genotype. There are also five other genotypes that are associated with varying clinical severity, and all have a majority of their hemoglobin as HbS [13]. HbSS, commonly referred to as sickle cell SS disease, is the most severe clinically, with the heterozygous HbS/β^o thalassemia genotype being similarly severe. HbSC has intermediate severity, HbS/β^+ has mild to moderate severity, and HbS/HPFH (hereditary persistence of HbF) and HbS/HbE demonstrate mild to no symptoms [14]. There exist several other genotypes that are exceedingly rare but do cause disease of varying severity. Those with sickle cell trait (heterozygous with HbA) have hemoglobin that is majority HbA [13]. Table 41.1 [15] displays the genotypes and phenotypes of different sickling disorders.

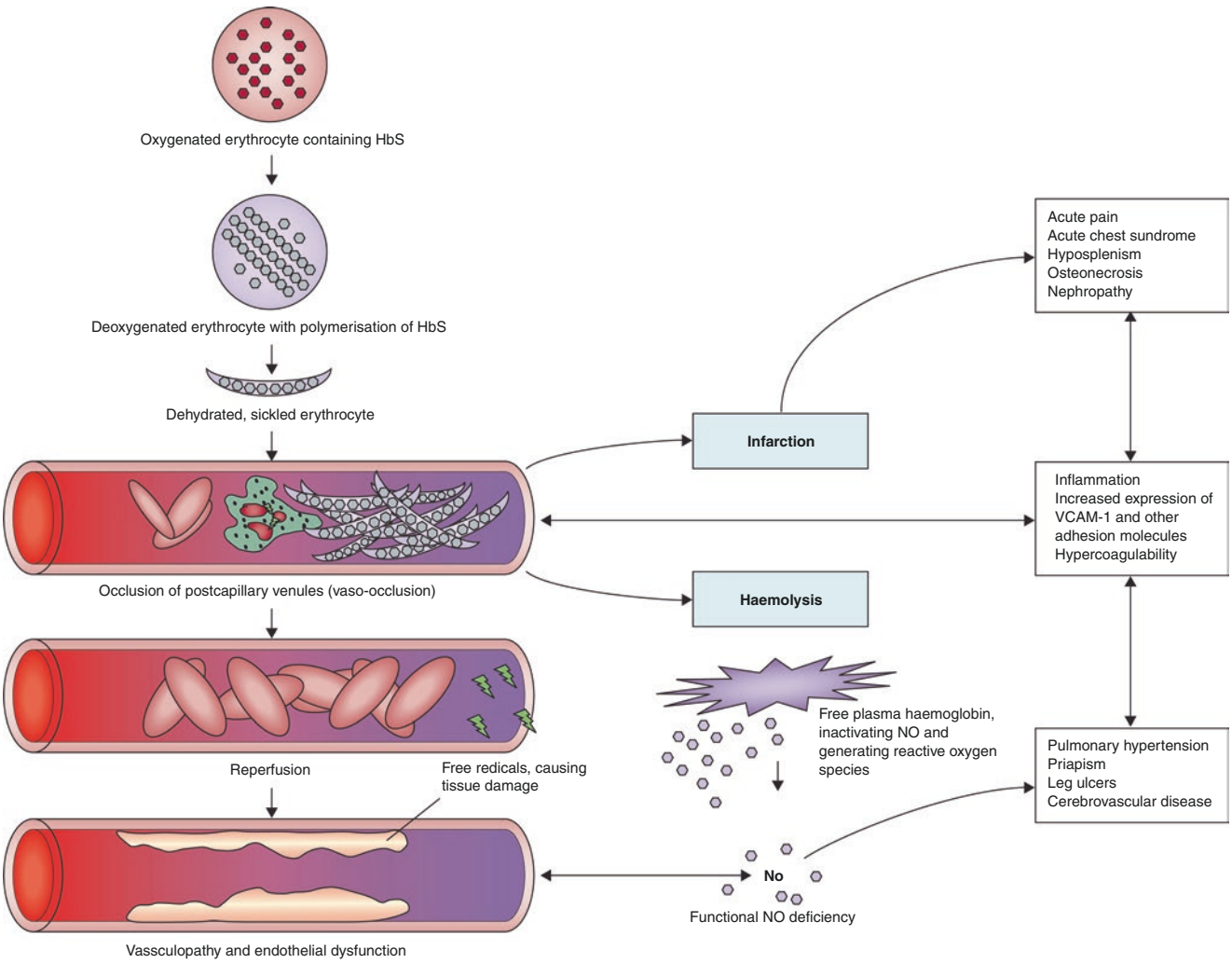

Fig. 41.1 Pathophysiology of sickle cell disease. (From Rees et al. [12], with permission of The Lancet and Elsevier)

Table 41.1 Genotypes and characteristics of different sickling disorders

	HbA (%)	HbS (%)	HbC (%)	HbF (%)	HbA_2 (%)	Clinical course
Normal	95–98	0	0	<1	<3.5	–
Trait conditions						
Sickle trait HbAS	55–65	30–40	0	<1	<3.5	Benign
Hemoglobin C trait	55–65	0	30–40%	<1	<3.5	Benign
β-Thalassemia trait	90–95	0	0	1–3	>3.5	Benign
Disease conditions						
Sickle cell anemia	0	80–95	0	5–15	<3.5	Severe
Sickle C disease	0	50–55	40–45%	<3	<3.5	Moderate
S/β^0 thalassemia	0	80–90	0	5–15	>3.5	Severe
S/β^+ thalassemia	10–25	70–80	0	<3	>3.5	Mild
S/other (Hb variant)	0	50–60	0	Variable	<3.5	Variable

Adapted from Ware et al. [15], with permission Elsevier

Epidemiology

Based on geographical distribution and genetic studies, the sickle cell gene is thought to provide protection against malaria infection by *Plasmodium falciparum* in heterozygotes [16]. Despite the length of time since this association was first proposed, the exact cellular mechanisms for this protection remain unclear [17]. Geographic distribution of HbS genotypes is based on the presence of malaria in a region and ensuing migration trends. While SCD is most common among people of African descent, it is also found among people of South Asian, Middle Eastern, and Mediterranean descent [18]. There are four African haplotypes and one Arab-Indian haplotype [12].

In the United States, prevalence of SCD is highest in the African American population (1 in 365 Black or African American) with the average age of death in all patients with SCD being 39 years [19]. With advances in medical care, survival to the age of 18 is now 93.9% with a mortality rate in pediatric patients of 0.52 per 100 patient years [20].

Clinical Presentations in the ED

Table 41.2 summarizes the various acute and chronic clinical presentations of sickle cell anemia [21]. Figure 41.2 shows the biochemical targets of potential treatments for SCD [21].

Pain in Sickle Cell Disease

While EPs most frequently encounter acute pain associated with SCD, they must become familiar with other types of pain that occur in patients with SCD (Table 41.3) [22]. The EP faces three important challenges. First, the EP must recognize other causes of pain that may masquerade as vaso-occlusive crisis (VOC) pain, in some instances representing dangerous conditions such as acute chest syndrome (abbreviated here as AChS to avoid confusion with acute coronary syndrome). However, adult patients with SCD can reasonably differentiate their VOC-related pain from other causes [23]. Second, the EP must be alert to other dangerous conditions that are not painful and are masked by the patient's preoccupation with their acute pain. Third, the EP must

Table 41.2 Clinical manifestations of sickle cell anemia

	Complication	Characteristics
Acute	Acute pain episodes (vaso-occlusive events)	Most common complication of SCD. Severity varies and may be manageable at home or require hospitalization
	Acute chest syndrome	Development of chest pain accompanied by fever, respiratory symptoms, and a chest X-ray with a new pulmonary opacity; associated with hypoxemia in severe cases
	Stroke	Both ischemic and hemorrhagic stokes may occur in adult SCD
	Thrombosis	Can occur in adult SCD, particularly during pregnancy and post-partum
	Liver complications	Acute pain in the right upper quadrant with jaundice requires workup to distinguish between acute cholecystitis, acute viral hepatitis, hepatic sequestration, and sickle cell intra-hepatic cholestasis
	Infections	Most frequently pneumonia, osteomyelitis, and urinary infections; may progress to or present primarily as sepsis
	Priapism	Compartment syndrome of the penis causing "stuttering" (short-lived, intermittent) or prolonged (lasting over 4 h) painful penile erections; can cause permanent erectile dysfunction
	Aplastic crisis	Exacerbated anemia accompanied by reticulocytopenia, usually caused by parvovirus B19 infection

(continued)

Table 41.2 (continued)

	Complication	Characteristics
Chronic	Hemolytic anemia	Normocytic, normochromic anemia; hemoglobin levels may vary between 6 and 10 g/dL, accompanied by reticulocytosis
	Functional asplenia	Splenic dysfunction and eventual autosplenectomy secondary to the splenic infarction that usually occurs during childhood
	Avascular necrosis	Can affect hip(s) or shoulder(s) causing early osteoarthritis and chronic pain
	Osteopenia and osteoporosis	Reduction of bone mass density occurs earlier than in the general population; is progressive and associated with hemolysis in SCD
	Pulmonary arterial hypertension	Exertional dyspnea or fatigue with chronic oxygen desaturation, caused by pulmonary artery lumen restriction and wall stiffening, linked to hemolysis, and associated with poor prognosis
	Gallstones/ cholelithiasis	Caused by augmented heme breakdown due to hemolysis
	Retinopathy	Proliferative retinopathy is relatively frequent, especially in HbSC disease and may cause blindness
	Nephropathy	Hyperfiltration and hyposthenuria occur early; incidence of microalbuminuria increases with patient age and can result in end-stage kidney disease
	Heart disease	Includes diastolic dysfunction with increased mortality, overt heart failure, and under-recognized acute myocardial infarction
	Leg ulcers	Development of ulcers in the maleolar and distal leg skin can be a recurring complication. These ulcers are painful, disfiguring, and are difficult to heal
	Neurological complications	Neurocognitive impairment is frequent, particularly in patients with previous stroke. Moyamoya syndrome may also occur, with proliferation of intracerebral blood vessels caused by stenosis or occlusion of cerebral arteries, increasing risk for acute cerebrovascular events

From Costa et al. [21], with permission Springer Nature

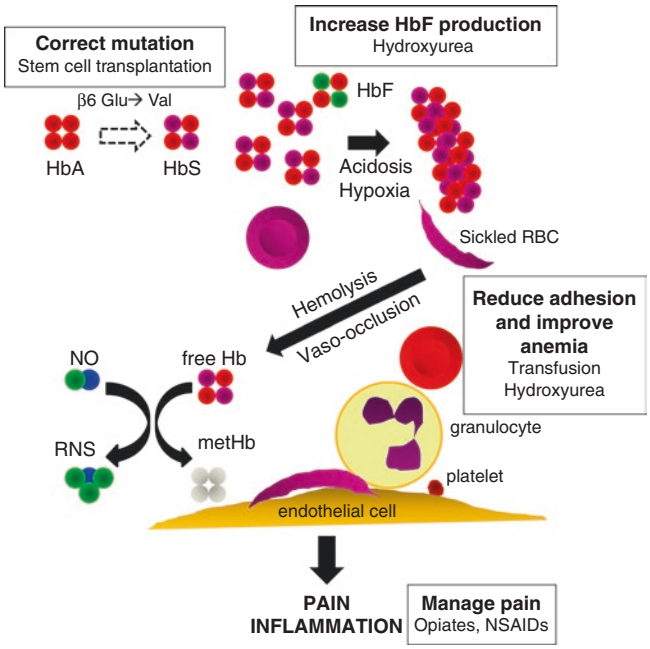

Fig. 41.2 Biochemical aspects of the management of sickle cell disease. (From Costa et al. [21], with permission Springer Nature)

Table 41.3 Types of pain in sickle cell disease

Intermittent pain syndromes
VOC with pain-free periods between recurrent episodes
Priapism
ACS
Splenic sequestration
Hepatic sequestration
Intrahepatic cholestasis
Dactylitis (hand-foot syndrome)
Intractable VOC with persistent pain between VOCs
Due to activation of the NMDA receptor
Due to central sensitization
Due to glial activation
Chronic pain syndromes
Leg ulcers
AVN
Chronic osteomyelitis
Osteoporosis/osteopenia
Neuropathy/neuropathic pain
Pain due to comorbidities
Mixed syndromes including two or more of the above types

From Ballas [22], with permission John Wiley & Sons
ACS acute chest syndrome, *AVN* avascular necrosis, *NMDA* N-methyl-D-aspartate, *VOC* vaso-occlusive crisis

promptly initiate analgesia and other therapy for the acute painful episode.

Chronic Pain in Sickle Cell Disease The Pain in Sickle Cell Epidemiology Study (PiSCES) found that in adult patients pain was reported in 56% of patient-days, with 29.3% of patients reporting pain on more than 95% of days logged [24]. Furthermore, this study identified that only 3.5% of patient-days were associated with utilization of healthcare services. These numbers are important to recognize in terms of reducing the biases that healthcare providers often harbor toward patients with SCD. The Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy (AAPT) initiative has developed diagnostic criteria for chronic sickle cell disease pain involving five dimensions [23]. These should be reviewed by providers in ED observation units and day units for sickle patients to gain familiarity with the spectrum of pain SCD patients experience. Table 41.4 outlines the AAPT criteria [23].

Table 41.4 American Pain Society Pain Taxonomy diagnostic criteria for chronic pain associated with sickle cell disease (SCD)

Dimension 1: Core diagnostic criteria
1. Diagnosis of SCD confirmed by laboratory testing
2. Reports of ongoing pain present on most days over the past 6 months either in a single location or in multiple locations
3. Must display *at least 1* sign:
Palpation of the region of reported pain elicits focal pain or tenderness
Movement of the region of reported pain elicits focal pain
Decreased range of motion or weakness in the region of reported pain
Evidence of skin ulcer in the region of reported pain
Evidence of hepatobiliary or splenic imaging abnormalities (e.g., splenic infarct, chronic pancreatitis) consistent with the region of reported pain
Evidence of imaging abnormalities consistent with bone infarction or avascular necrosis in the region of reported pain
4. There is no other diagnosis that better explains the signs and symptoms
Chronic SCD pain diagnostic modifiers:
We propose three diagnostic modifiers to indicate subtypes of chronic SCD pain
1. Chronic SCD pain without contributory disease complications is used if there is no evidence of contributory SCD complications on the basis of either clinical signs (e.g., presence of leg ulcers) or test results (e.g., imaging abnormalities)
2. Chronic SCD pain with contributory disease complications should be used if there is evidence of contributory SCD complications on the basis of clinical signs or test results
3. Chronic SCD pain with mixed pain types should be used if there is evidence of contributory SCD complications (e.g., avascular necrosis) on the basis of clinical signs or test results and there is pain also occurring in unrelated sites (e.g., arms, back, chest, or abdominal pain)

From Dampier et al. [23], with permission Elsevier

Vaso-occlusive Crisis and Acute Painful Episodes Vaso-occlusive crisis (VOC) is the most common ED presentation of SCD. Patients with HbSS or HbSβ0 experience frequent VOCs, while those with sickle cell trait do not experience typical VOCs [25]. Microvascular occlusion (the cardinal pathophysiologic cause of acute pain) leads to ischemia and hypoxia. This is followed by tissue and vascular damage and inflammation, with release of inflammatory mediators, all of which activate nociceptors [22, 26]. Reperfusion intensifies the inflammation and resultant pain [3, 4, 6]. Patients experiencing frequent pain crises (more than three per year) are at higher risk for complications including a higher mortality rate [23].

Classically, acute pain from VOC is described in the back or extremities, although it may occur elsewhere. It may be migratory and is usually continuous and progressive. VOC pain occurs less frequently elsewhere, such as in the chest, where it may create diagnostic overlap with acute chest syndrome and other causes of chest pain. Pain from VOC should be distinguished from two other patterns of pain experienced by patients with SCD: acute flare of chronic pain and neuropathic pain. Generally, the major focus for the EP is upon management of acute painful episodes caused by VOC.

There are no reliable signs or tests to indicate the presence or absence of VOC or pain associated with VOC. Patients' self-reported pain scores do not reliably correlate with changes in vital signs, such as tachycardia, hypertension, or tachypnea, that may be associated with pain in other clinical contexts. Hemoglobin, hematocrit, and reticulocyte measurements do not serve as markers for pain; neither do some more recent tests such as inflammatory cytokines [26]. Further, patients may exhibit behavior which EPs consider inconsistent with pain, including walking, engaging in conversations, or having a calm appearance while still reporting high levels of pain [3, 5, 27]. Laboratory tests should be ordered for patients who are being admitted and for other indications that may be considered.

Opioids have been the mainstay of analgesia for acute painful episodes over the past century. Meperidine was commonly used in the past but is no longer a commonly available or utilized medication because it is metabolized to normeperidine and has been linked to emotional and behavioral changes as well as seizures due to renal excretion and a long half-life [28–30]. More recently morphine, fentanyl, and hydromorphone became the medications of choice in EDs. However, with the recent opioid crisis and related stigma and addiction concerns, there is an emphasis on using these in an incremental and targeted manner.

Contemporary management of acute painful episodes is outlined in Table 41.5. Key goals include prioritization of these patients in triage, early and adequate analgesia, and frequent repeat dosing until pain is controlled [3, 22, 25–31].

Table 41.5 Emergency department (ED) management of sickle cell disease-related pain

Triage
Triage as high priority ESI level 2
Assess for complications and administer first dose of analgesic within 30 min of triage or within 60 min of registration
Route of administration
Oral route preferred for initial dose
Intranasal can be an alternative for appropriate medication
Intravenous should be used for second-line therapy
Avoid intramuscular route due to unpredictable pharmacokinetics
Medications
Opioid naïve: NSAIDs such as ibuprofen and ketorolac for mild-moderate pain, with oral immediate-release morphine or intranasal fentanyl for severe pain
Opioid tolerant: Oral immediate-release morphine based on home dose, with intranasal fentanyl as an alternative
Intravenous morphine if unable to tolerate or failed oral administration
Pain/sub-dissociative dose ketamine for persistent/uncontrolled pain
Avoid meperidine and hydromorphone
Reassessment
Within 30 min
Use capnography if available before initiating additional or higher doses of morphine
Consider admission or placement in observation unit if pain is not controlled within 90 min with adequate dosing
Adjuncts
Ondansetron for nausea or vomiting
Oral diphenhydramine for itching associated with opioids (with first dose only)
Acetaminophen as an adjunct for pain relief
Consider non-pharmacologic approaches such as heat, acupuncture, etc.
Other therapies
Intravenous fluids: routine fluids not indicated in the ED if euvolemic – bolus only if hypovolemic
Oxygen: only if hypoxic (oxygen saturation less than 92%)
Nitric oxide: vasodilatory effect, but limited data on benefits with potential risks
Hydroxyurea: increased HbF and reduces frequency of VOC

ESI Emergency Severity Index, *NSAID* non-steroidal anti-inflammatory drug, *VOC* vaso-occlusive crisis

Avoid using the intramuscular route and administer fluids only to patients who are hypovolemic.

Patients with acute painful episodes may be discharged if their pain is adequately controlled and they expect, based on past individual experience, that it will remain adequately controlled with ongoing use of their outpatient analgesic regimen. There is no evidence-based fixed number of doses of opioid medication established as a threshold for admission decisions, and EPs should judge the necessity of admission on clinical grounds, balancing the benefits of pain control with parenteral opioids and adjuvants against the well-known risks of hospitalization.

Day clinics are a complement and alternative to traditional inpatient therapy for acute painful episodes [5, 31]. Day clinics are less resource intensive than EDs, with less associated pressure on length of stay and more room to achieve pain control and discharge to home without repeat presentation. Day clinics can additionally complement outpatient hematology clinics as part of a medical home for patients with SCD, providing a multidisciplinary approach beyond acute pain management.

Acute Chest Syndrome

Acute chest syndrome (AChS) is defined as the appearance of a new pulmonary infiltrate on chest radiography accompanied by a fever and respiratory symptoms including cough, tachypnea, and chest pain [32, 33]. It is hypothesized that AChS is the result of hypoxia and an inflammatory mediator-induced increase in adhesion of the pulmonary microvasculature to sickled erythrocytes. This is coupled with a reduction in NO that would normally counteract this [34, 35]. The most common symptoms in patients with AChS are fever (80%) and cough (62–74%), with rales being the most common finding on physical exam (48–76%) [33]. Table 41.6 displays clinical and laboratory characteristics of acute chest syndrome [33].

Table 41.6 Select clinical and laboratory characteristics at diagnosis of acute chest syndrome

	CSSCD	MACSSD
Symptoms at diagnosis, %		
Fever	80	80
Cough	74	62
Chest pain	57	44
Tachypnea	28	45
Pain in arms and legs	NR	37
Pain in ribs and sternum	NR	21
Pain in abdomen	NR	35
Reactive airway disease	NR	13
Neurologic dysfunction	NR	4
Physical findings/lab investigations at diagnosis		
Respiratory rate >30/min, %	18 (>40/min)	67
Wheeze, %	10	26
Rales, %	48	76
Normal auscultation, %	35	NR
Mean Hb (g/dL) in HbSS patients	7.9	7.7
Mean leukocyte count (103/mm^3)	21.1	23
Mean O2 saturation	NR	92
Mean Pa O2 (mm Hg)	71	70
Effusion (% adults)	21	36
Effusion (% children <10 y)	3	34
Bacteremia, %	3.5	NR
Admitted for reasons other than		
Symptoms of ACS, %	42	48
Duration hospital stay for adults (d)	9	12.8
Duration hospital stay for child (d)	5.4	9.7

From Stuart and Setty [33], with permission Wolters Kluwer
CSSCD Cooperative Study of Sickle Cell Disease, *MACSS* Multi-Center Acute Chest Syndrome Study Group, *ACS* acute chest syndrome, *NR* not recorded

While a significant portion (45.7%) of cases of AChS are due to unknown etiologies, 30% of AChS cases yield a documented infection, and about 9% are attributed to a pulmonary fat embolism (which in turn could be due to infection) and 16% to pulmonary infarction (not caused by infection or fat embolism) [35]. Hypoventilation due to two common clinical scenarios puts the patient at risk for AChS: splinting (pain) and/or opioid analgesic side effects (somnolence) [33]. Pulmonary edema caused by intravenous hydration may lead to AChS, but the data is not conclusive. Pulmonary thrombosis occurs in about 17% of cases with AChS, but it is unclear if it is a cause of AChS [36]. Additionally, the use of clinical decision rules such as the revised Geneva score and d-dimer testing have not been found to be useful in patients with AChS [36].

Initial management of AChS includes empiric antibiotics (cephalosporin and macrolide – to ensure coverage of chlamydia and mycoplasma); however, antibiotics do not appear to have a significant effect on patient outcomes [25]. In a single, small randomized controlled trial, dexamethasone use was shown to have a short-term benefit on hospital length of stay, need for transfusions, number of opioid doses, and clinical condition [37]; however, with longer follow-up, results were inconsistent. There is wide variability in dexamethasone use between hospitals, and in the absence of larger randomized clinical trials, it is difficult to determine its efficacy with any precision [38]. Incentive spirometry plays a significant role in the prophylaxis and treatment of AChS [25]. Pain medications and intravenous hydration should be administered judiciously due to their risk of worsening the condition.

Blood transfusion has been used effectively in the United States for treatment of AChS, but a significant improvement in mortality rate has not been noted when compared to Europe, where it is not used as routinely [35]. Additionally, substantial increases in hemoglobin levels can increase viscosity, thereby raising the risk of complications. Exchange transfusion may be considered in patients with a baseline "high" hemoglobin or those with "multilobe involvement, persistent or worsening hypoxemia, neurologic abnormalities, or multi-organ failure" but has also had mixed results [25, 35, 39, 40]. Both transfusions retain a "Strong Recommendation" from the National Heart, Lung, and Blood Institute's Expert Panel but with low-quality evidence [25].

The role of anti-coagulation in AChS patients with pulmonary thrombosis remains unclear, but EPs would be hard-pressed to avoid anti-coagulation if CT findings are consistent with a pulmonary artery occlusion. Nitric oxide inhalation and steroids may also be used in the management of AChS, but at present, these therapies should be considered experimental [35].

Disposition of these patients should be dictated by their clinical status. While increasing age is associated with worse outcomes (adults generally do worse than pediatric patients) and up to 3% of patients with AChS die, absolute predictors of bad outcomes are difficult to define. The best predictors of bad outcome are extensive lung involvement on x-ray, a platelet count of less than 199,000/mm^3, and cardiac disease as a comorbidity [35]. All patients with AChS should initially be admitted to a monitored setting (not necessarily an intensive care unit).

Fever and Infection

Patients with SCD are at high risk for infections with encapsulated organisms due to functional asplenia, as well as a functionally immunocompromised state (increased bone marrow turnover and altered complement activation) [4]. Penicillin prophylaxis in children and widespread use of the pneumococcal vaccine have made tremendous headway in reducing the incidence of bacterial infections and sepsis [25]. However, EPs must remain aggressive in working up any SCD patient presenting with a fever while keeping in mind that their reduced ability to mount an inflammatory response may limit leukocytosis or even an elevated temperature.

A low threshold should be employed to order a complete blood count (CBC), chest x-ray, and urinalysis at minimum. If no source if identified, consideration should be given to obtaining blood and urine cultures, performing a lumbar puncture, evaluating for potential arthrocentesis, and initiating empiric antibiotics. Workup and treatment should be even more aggressive in pediatric patients since the risk of overwhelming *Streptococcus pneumoniae* sepsis is high [25, 41].

Admission to the hospital should be strongly considered for ill-appearing patients with SCD and a temperature ≥103.1 °F (39.5 °C) [25]. Outpatient management with administration of parenteral long-acting antibiotics may be considered in select patients with reliable follow-up (within 24 h) as long as they defervesce, have never been septic, and have a normal chest radiograph, oxygen saturation, baseline white blood cell (WBC) count, platelet count, and hemoglobin.

Pulmonary Hypertension

Pulmonary hypertension (PHTN) has an incidence of 6–10% and a mortality rate of 2–5% [13]. PHTN is thought to be due in large part to changes in medial smooth muscle and endothelial cells. The key clinical finding is reduced exercise

capacity (45% of patients are New York Heart Association class III or IV) [13]. Diagnostic findings include an elevated N-terminal pro-brain natriuretic peptide (NT-proBNP), an elevated tricuspid valve regurgitant jet velocity on echocardiography, and elevated pulmonary pressures on right heart catheterization.

Currently there is no approved and effective therapy to manage PHTN in SCD patients. Sildenafil, used in non-SCD-related PHTN, has been studied but was found to increase acute pain episodes [13].

Cerebrovascular Accident

While strokes are unusual entities in the general pediatric population, they are relatively frequent in children with SCD and more common in children than adults with SCD [12, 13]. Cerebrovascular accidents (CVA) can occur in children as young as 2 years of age, with 11% of patients with SCD having a stroke by 20 years of age [12]. However, silent cerebral infarcts (SCI) associated with small-vessel disease are more common than overt strokes with 34% of SCD patients having evidence of SCI by age 14 [13]. Symptomatic patients exhibit vasculopathy primarily in the distribution of mid- to large-sized arteries (distal internal carotid and middle cerebral arteries) which is triggered by anemia, leukocytosis, hypoxia, and impaired regulation of blood flow [12, 13].

The Stroke Prevention Trial in Sickle Cell Anemia (STOP) study showed that in patients with elevated transcranial Doppler velocities, prophylactic blood transfusion to maintain HbS less than 30% could reduce the risk of stroke to less than 1% [42]. Exchange transfusion is recommended in SCD patients with an image-confirmed acute CVA [25, 43]. Additionally, myeloablative bone marrow transplant appears to offer a significant benefit in limiting cerebral vasculopathy and, in turn, risk for a CVA [13]. Tissue plasminogen activator (tPA) has not been studied specifically in patients with SCD. Therefore, the determination of whether to treat SCD patients presenting with a CVA with tPA should be made in consultation with a neurologist and hematologist [4].

Pulmonary Embolism

Patients with SCD should intuitively seem susceptible to venous thromboembolism (VTE) given their increased coagulability, endothelial dysfunction, and impaired blood flow (Virchow's triad) [44, 45]. Indeed, the incidence of pulmonary embolism (PE) is higher in patients with SCD. There is a 50–100-fold increase in annual incidence in inpatients with SCD compared to those without SCD [44, 46, 47]. VTE is present in 50% of autopsies of patients with SCD, and yet only 5% of these are detected clinically [46]. Additionally, patients with AChS have a reported PE prevalence rate approaching 17%, and PE may be a contributing factor to the pulmonary hypertension seen in patients with SCD [36]. Despite this, inpatients with SCD undergo fewer chest computed tomography (CT) angiography tests for PE compared to those without SCD [46].

Unfortunately, several clinical prediction rules for VTE are unreliable in the setting of SCD since symptoms of AChS and VOC may overlap with those of VTE. D-dimer testing is also of limited utility since elevated D-dimer levels are found in the vast majority (92%) of patients with VOC [44, 45].

Therefore, a high index of suspicion for VTE must be maintained when evaluating patients with SCD. Computed tomography pulmonary angiography (CTPA) and ventilation-perfusion scanning are both reasonable options for the further workup of pulmonary embolism [48, 49]. Despite concerns and reports regarding intravenous contrast inducing nephropathy and/or increasing sickling of erythrocytes, there is data indicating no difference in adverse events compared to patients without SCD. Lower extremity venous duplex evaluation should also be considered to reduce radiation risk and the risk of other complications in patients with VOC.

Acute Coronary Syndrome

The literature indicates that patients with SCD have minimal atherosclerosis of the large coronary arteries [50–53]. This is despite case reports and autopsy series which reveal findings of myocardial infarction presumably from vaso-occlusive effects on coronary microcirculation [53–55]. Therefore, acute coronary syndrome (ACS) should be considered in the differential for patients with SCD presenting with cardiac symptoms regardless of age (since VOC at the microvascular level is not age dependent).

Since SCD by itself does not result in a baseline increase in cardiac biomarkers (troponin-I, troponin-T, and creatinine kinase isoenzyme MB) [53, 56], an appropriate strategy would be to evaluate patients that are deemed at risk for ACS with serial electrocardiograms and serial cardiac biomarkers. Stress testing or cardiac CT angiography (CCTA) should be considered based on national guidelines.

The treatment of acute ST-elevation myocardial infarction should err on the side of interventional treatment since thrombolytics have not been studied specifically in patients with SCD. However, when interventional options are unavailable in a timely manner, thrombolytics should be considered in consultation with a hematologist and cardiologist when possible.

Renal Complications

Renal complications are extremely common in SCD with 30% of adults developing chronic renal failure [13]. Pre-renal, post-renal, and intrinsic renal factors all contribute to this dysfunction. Acute kidney injury can occur during an acute VOC due to low partial pressure of oxygen, low pH, and high osmolality in the renal medulla which all contribute to erythrocyte dehydration and vaso-occlusion [12, 25]. Diffuse vaso-occlusion can result in multisystem organ failure including renal complications.

Microalbuminuria and proteinuria are common diagnostic findings [14, 25]. It is important to avoid nephrotoxic drugs and monitor renal function on a regular basis. ACE inhibitors are used prophylactically (including in children) to reduce the progression of disease, while transplantation has significant benefits in survival over dialysis [12].

Ocular Complications

Proliferative retinopathy is the most common ophthalmologic complication of SCD (more common in HbSC – as high as 70%) and results from occlusion of the peripheral retinal vasculature [13, 14]. Permanent loss of vision can occur from ocular complications not only due to progression of this proliferative sickle retinopathy but also from complications of trauma, infection, and VOC.

Hyphema can lead to significant complications in patients with SCD and also with sickle cell trait since sickling is more likely to occur in the hypoxic and acidotic anterior chamber with resultant outflow tract obstruction. The elevated intraocular pressure (IOP) that results can cause central retinal artery occlusion and infarction of the optic nerve [57, 58]. Presence of a significant hyphema warrants ophthalmologic consultation with possible surgical drainage [59, 60].

Orbital infarction, although rare, can also occur in SCD patients experiencing a VOC, and compression of the optic nerve as well as nerves affecting extraocular movements are also possible [61, 62]. Surgical intervention is indicated if symptoms progress rapidly.

Splenic Sequestration

Splenic sequestration is a potentially catastrophic complication of SCD and is characterized by an acute drop in hemoglobin that can cause circulatory collapse. It is more common in the pediatric population, especially with HbSS, since they have not yet auto-infarcted their spleen [14, 41]. The mechanism for this entity involves sickled erythrocytes becoming trapped within the spleen and thereby being removed from the circulatory system, manifested in laboratory testing as a profound anemia.

EPs must consider this entity when presented with an adult or child with acute splenic enlargement and circulatory collapse. Splenic sequestration can be differentiated from other causes of anemia associated with SCD (hemolysis, red cell aplasia) based on a combination of laboratory tests: severe anemia, elevated reticulocyte count, and findings of hemolysis (elevated indirect bilirubin, ALT, and LDH) [41]. Guidance regarding the management of SCD patients with splenic sequestration is limited, but transfusion (without over-transfusion) and splenectomy are being advised, in addition to observation based on the patient's clinical status [25]. Eventually a splenectomy is critical since splenic sequestration recurs at a rate of nearly 50% [14].

Priapism

Priapism associated with SCD is typically of the low-flow type associated with stasis, hypoxia, and ischemia, with about 35% of boys/men affected [14, 63]. Conservative management with fluid hydration and analgesia are an appropriate first step, with medical management including injection of phenylephrine into the corpora cavernosa, subcutaneous terbutaline, and/or oral pseudoephedrine. Interventional approaches such as aspiration and irrigation with alpha-adrenergic agents are an appropriate next step. If these therapies are unsuccessful, then emergent urologic consultation for possible shunting is recommended.

Hepatobiliary

Biliary sludge and cholelithiasis/choledocholithiasis are common in SCD patients due to chronic hemolysis and increased bilirubin turnover [64]. Gallstones are noted on ultrasound in up to 70% of patients [25]. Asymptomatic patients should be managed conservatively, while surgical cholecystectomy, including laparoscopic approaches, has good outcomes [65].

As with splenic sequestration, hepatic crisis and hepatic sequestration can occur and require aggressive management with hydration, rest, and close observation [25]. Exchange transfusion has demonstrated positive results [66]. Of note, frequent transfusions can also result in hemosiderosis or hemochromatosis.

Avascular Necrosis (AVN)

Sickling results in occlusion of capillaries which in turn causes inadequate blood supply with consequential bone

death. The femoral heads are common sites of this osteonecrosis. About 50% of patients with HbSS demonstrate some avascular necrosis by age 33 [67]. Pain control and physical therapy are the mainstays of treatment, with surgical treatment for symptomatic patients with advanced AVN [25].

Aplastic Crises

Commonly seen in children, aplastic crisis presents with gradual onset fatigue, shortness of breath, and fever. Patients can present with tachycardia and even florid heart failure. Parvovirus B19 has been identified as the inciting infection [68], causing an interruption of erythropoiesis via destruction of erythrocyte precursors and resulting in severe anemia and cardiovascular decompensation. This self-limited infection typically lasts 7–10 days and results in lifelong immunity [14].

Controversies in the Management of Sickle Cell Disease

Acute Pain

Unfortunately, stigma and judgment often influence the diagnosis and management of SCD patients who present to the ED in pain. It is important to remember that these patients can experience similar painful disease processes as patients without SCD and failure to recognize non-SCD-related conditions can result in poor outcomes. As mentioned previously, patients are generally able to ascertain if the acute pain they are feeling is typical of prior VOC episodes. Additional testing should be considered when patients complain that a painful episode is different in character (not just severity) from typical episodes. In some cases, VOC may be triggered by an unrelated diagnosis, but the acute pain from the VOC may mask this underlying condition. Therefore, it is important that EPs proactively set aside their biases and approach patients with SCD in an open-minded and non-judgmental manner.

Physicians treating patients with SCD are at specific risk for cognitive biases, also known as cognitive dispositions to respond. Examples of cognitive bias include being overcommitted to a given diagnosis, failure to consider alternative diagnoses, continuing with a diagnosis reached by others, being overly influenced by past patient experiences, ending the diagnostic workup prematurely, and being influenced by context or patient characteristics [69, 70].

Opioid Crisis and Implications for the Care of Patients with SCD

Over the past 10 years, the opioid crisis in the United States has received increasing attention. Given that that from 1999 to 2018 over 400,000 people died from an opioid overdose, that 2 out of 3 drug overdose deaths in 2018 involved an opioid, that nearly 47,000 people died from opioid overdoses in 2018, and that 32% of those deaths involved prescription opioids [71, 72], there is immense pressure on emergency physicians to curtail the use and prescription of opioids. However, the challenges related to the objective assessment of pain as well as pressures related to patient satisfaction scores and the emphasis on early pain management by regulatory agencies have placed emergency physicians in a quandary regarding the appropriate management of SCD patients presenting with acute pain.

However, prudent strategies can guide emergency departments and EPs in this regard. First, it is helpful to develop departmental and/or institutional evidence-based guidelines in a collaborative manner with a variety of personnel involved in the care of patients with SCD. Second, these guidelines should recognize the need to differentiate opioid-naive from opioid-tolerant patients while also acknowledging that the latter group is not simply "addicted" to opioids but that there is a physiologic basis for the dependence that has developed over time. Finally, prudent limitations such as avoidance of intramuscular administration and minimizing use of intravenous hydromorphone and diphenhydramine while still utilizing opioids in the management can guide EPs in appropriately caring for patients with VOC.

Additionally, high utilizers of emergency department services should be managed proactively with a diverse care team and individualized care plans to ensure that the patient's needs are met while being judicious in the use of opioid medications. Increasing interoperability of electronic medical records and prescription drug monitoring programs are helpful in assessing a patient's use of healthcare resources and potential overuse of opioids. Goals driven by care plans and collaborations between EPs and outpatient physicians are shown in Table 41.7 [73].

Intravenous Fluids

Given that erythrocyte dehydration plays a significant role in the pathophysiology of SCD, hydration has long been a com-

Table 41.7 Goals in promoting care coordination and continuity

Patient received coordinated, comprehensive care
Patient keeps regular appointments (for patients with three or more ED visits per year, it is recommended they have at least four scheduled outpatient appointments per year, with a goal of not missing more than one appointment except when missed because of hospitalization)
Patient is compliant with health promotion and disease management programs
Patient abstains from using illicit opioids
Patient obtains opioid prescriptions from a single practice

From Lovett et al. [73], with permission Elsevier

ponent of therapy. However, while isolated and suboptimal studies have shown a potential benefit to intravenous hydration during VOC and for other complications, there is inadequate data to assess the safety of aggressive hydration [74]. Additionally, there are reports linking excessive fluid administration to the development of atelectasis [75], and this in turn to AChS. Thus, it is recommended that boluses of intravenous fluids be reserved for suspected or proven hypovolemia or hypertonicity [4].

Blood Transfusion

Erythrocyte transfusions, with the goal of reducing HbS to less than 30%, are indicated in the urgent management of acute anemia, AChS, acute neurological deficits, multi-organ failure, and perioperative management [12, 25, 76]. However, care must be taken to avoid volume overload and increased blood viscosity associated with transfusion. Transfusion is not recommended in patients with asymptomatic anemia and those with acute kidney injury in the absence of multisystem organ failure [25].

Transfusions may be considered in patients hospitalized with complications of SCD (e.g., AChS, cerebral infarction, ACS) but not simple VOC. Anemia should not be overcorrected with a goal of no more than 10 g/dL with care be taken to use leukocyte-reduced blood that is matched for all relevant antigens (Rh, C, E, and Kell) [25, 33]. Regular, long-term transfusions are beneficial in the prevention of strokes in pediatric patients, but carry risks of alloimmunization and iron overload, and hence should be coordinated with the patient's hematologist [20, 25]. Figure 41.3 represents

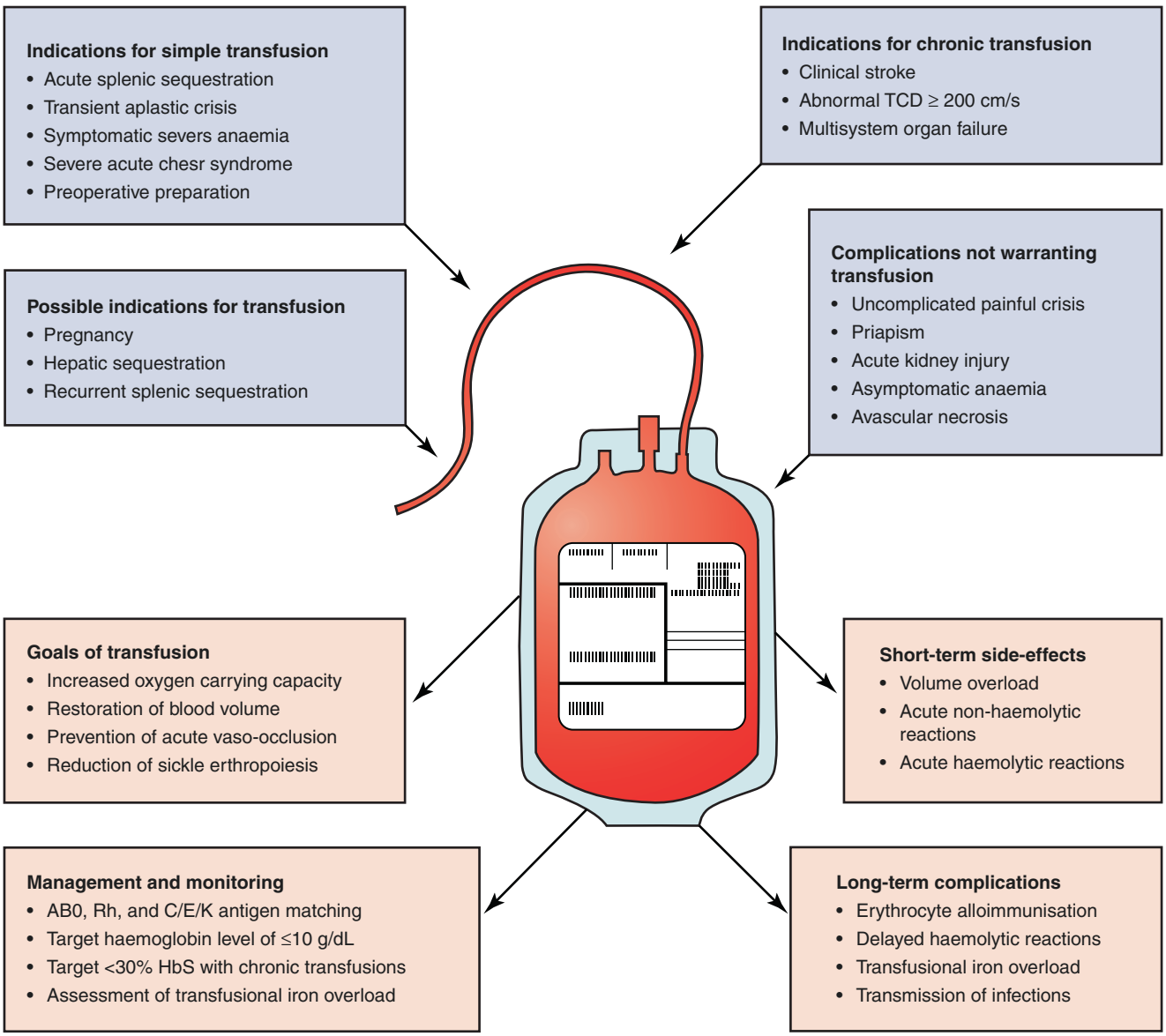

Fig. 41.3 Indications and goals for blood transfusion. (From Ware et al. [15], with permission The Lancet and Elsevier)

current recommendations regarding transfusion therapy for acute complications of SCD [15].

Hydroxyurea (Hydroxycarbamide)

Hydroxyurea is a ribonucleotide reductase inhibitor that can increase HbF levels, in turn inhibiting polymerization of deoxygenated HbS [77–79]. Additionally, it triggers increased donation of NO and a reduction in erythrocyte adhesiveness and leukocyte count [13, 25, 79]. Results of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) were promising with a 50% reduction in painful episodes, reduced need for blood transfusions, and lower mortality rate at 9 years [80]. While a potentially effective therapy, it requires time to trigger an increase in HbF and should be given per a standardized protocol – it is therefore not a realistic option for acute ED management, but should be strongly considered if the patient is being cared for in an ED observation unit [25].

Looking Ahead

It is striking to note the dearth of high-quality evidence, especially randomized controlled trials (RCTs), related to the management of SCD. Sickle cell disease exemplifies the potential racial and ethnic disparities that exist in healthcare spending and research, as well as stigmas associated with patients afflicted with it. The most tangible hope for a cure exists with hematopoietic stem cell transplantation (HSCT) but is feasible in only a small proportion of patients with SCD [81].

Several other therapies are under early investigation (phase 1 and 2 trials) [15], and gene therapy has shown promise; however, introduction to clinical practice remains years away [82].

Summary

Sickle cell disease is a genetic disorder commonly encountered by ED providers. Acute painful episodes are by far the most common reason for ED visits. Early and aggressive pain management is a key priority in these visits; however, EPs must also actively seek to diagnose other emergent diagnoses in patients with SCD, including AChS and infection, and differentiate them from VOC. EPs should be especially aware of cognitive biases that may misdirect the diagnostic process.

Bolus administration of intravenous fluids should be considered only for hypovolemic patients. Blood transfusion may be considered to reduce the percentage of HbS, but close attention must be given to its associated risks – impact on volume status and viscosity. Conditions such as acute coronary syndrome, pulmonary embolism, and cerebrovascular accident must be considered in the evaluation of patients with SCD, and while management is guided by the standard of care for the individual conditions, early consultation with hematology is imperative.

Finally, we cannot over-emphasize the importance of coordinating care with hematology and the outpatient team in the effective emergency and long-term management of patients with sickle cell disease.

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Radiological and Nuclear Terrorism

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Carol J. Iddins, Jason E. Davis, Ronald E. Goans, and Cullen Case Jr.

Introduction

Recent world events and political tensions are again bringing attention to the possibility of a nuclear incident, including a detonation. Radiological materials are ubiquitous and are found in most cities throughout the country at academic institutions, hospitals, and many businesses and in industrial settings. Nuclear materials are more difficult to access because of their scarce nature and the security of the settings in which they are found. A significant radiological or nuclear (R/N) incident in the Unites States will require activation of local, state, territory, regional, and national government assets. Initially, ad hoc triage and treatment areas will rise up in the moderately to lightly damaged zones. Patients will undergo mass casualty triage and stabilization before medical evacuation to subsequent higher levels of care. This will require subject matter expert advice and response as the size and circumstances of the incident unfold. Initial mass casualty triage should be done to sort the populations who will require minor interventions, admission to the hospital, and possibly eventual intensive care and those who may have an extremely dire prognosis and may require comfort or hospice care. The hematologist-oncologist will be among those with the expertise to effectively treat those patients who will experience bone marrow aplasia as part of radiation exposure that is higher than 1–2 Gray (Gy). Acute radiation syndrome (ARS) is the complex of organ system injuries that occur from the radiation exposure. The organ systems show a classical clinical prodrome that correlates to radiation exposure dose. This syndrome will affect bone marrow, gastrointestinal, cutaneous, pulmonary, and neurovascular systems. These patients will require the expertise of intensivists and those experienced in managing systemic inflammatory response syndrome (SIRS), multiple organ dysfunction (MOD), and multiple organ failure (MOF) that may result. This chapter provides an overview for the hematologist-oncologist in managing patients who may present after an R/N incident.

Some understanding of the mechanisms of damage incurred from radiation is helpful in managing these patients. This is not routinely included in our medical or graduate medical education. Many oncologists and radiation oncologists deal with radiotherapy adverse effects, but, otherwise, most physicians never manage a patient from a radiological incident. A review of some important terms and topics is included for better understanding of the disease processes.

Radiological materials have many uses in academia, medicine, and industry. They may be used in the initiation or attempted initiation of an energetic chain reaction of fissionable materials. Small quantities of fissionable nuclear materials generally pose more of a chemical hazard than a radiological hazard. If sufficient quantities of fissionable material are present in the correct geometry, a chain reaction is initiated resulting in the release of immense amounts of energy and the production of highly radioactive isotopes. Nuclear fission supplies the destructive potential of improvised nuclear devices (IND) (a terrorist nuclear bomb) and more sophisticated nuclear weapons. Fission is also the process used to generate heat for the production of electricity in nuclear power plants (NPPs). In fission reactors, steam generated from the nuclear process is used to turn a turbine which, in turn, rotates a generator [1].

Measurement of Radioactivity Radioactivity, the activity of a radiation source, is the term used to describe how much

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energy is being released by radioactive material in a given time. Radioactivity or activity is measured in curies (Ci) in the English measurement system or the becquerel (Bq) in the SI system (SI = International System of Units or Système International). A Bq is equivalent to one disintegration of an atomic nucleus per second. A Ci is equivalent to 3.7×10^{10} disintegrations per second (dps) and is based on the decay rate of radium-226. A Bq is so small that it is much more common to see units in multiples of Bq such as megabecquerels (MBq), gigabecquerels (GBq), etc. Likewise, a curie is so large that it is much more common to see units in fractions of Ci such as millicuries (mCi), microcuries (μCi), etc.

Units of Dose Measurement The unit rad is often used in the English system to describe the amount of ionizing radiation that is absorbed in a cell, tissue, organ, or the body. It is equivalent to 100 ergs of energy deposited in 1 g of tissue. The gray (Gy) is equivalent to 1 J of energy deposited in 1 kg of tissue. One Gy is equivalent to 100 rad. The rem (roentgen equivalent man) is a unit of equivalent dose which is used to measure the long-term biological risk related to ionizing radiation exposure (in the USA). The sievert (Sv) is the international unit (SI) for equivalent dose. One Sv is equivalent to 100 rem. The terms Gy and Sv will be used.

Radiological and Nuclear Scenarios of Concern

Key to understanding radiological and nuclear incidents are the types of injuries and illnesses that they can cause. There are many occupational and medical exposures occurring with more frequency. However, the following radiation scenarios are of concern for emergency care responders:

- Radiological exposure device (RED)
- Radiological dispersal device (RDD)
- Improvised nuclear device (IND)
- Nuclear weapon detonation (NWD)
- Nuclear power plant (NPP) incident

Radiological Exposure Device (RED)

A RED is any radioactive material or an object containing radioactive material that can expose people to radiation without their knowledge. These materials may be inadvertently left in an accessible area or may be intentionally placed in a public space with the intent to cause harm to one or more people. The radiation-induced injuries and illnesses that may result from exposure or touching the source vary, depending upon the nature of the source, the radiation emitted, and the energy of the radiation emitted. It is possible for an RED to cause severe damage up to, and including, ARS, as well as cutaneous radiation injuries (CRI) with damage to the skin and deeper tissues and organs.

Radiological Dispersal Device (RDD)

A radiological dispersal device (RDD) is any device that spreads radioactive material in the environment with the intent to cause panic, destruction, damage, or injury. A "dirty bomb" is one type of RDD, in which explosives are used as the mechanism to disperse the radioactive material. Radioactive materials needed to produce an RDD can be obtained from industrial, commercial, medical, and research applications. An explosive RDD may result in the immediate threat to human life. Hazards will occur from fire, smoke, shock (physical, or thermal), and debris from the explosion. The long-term consequences of an explosive RDD could involve increased risk of cancer to exposed individuals resulting from direct exposure to radioactive materials, the inhalation of radioactive materials, and potential contact with other hazardous materials present at the scene. In most plausible scenarios, the radioactive material would not result in acutely harmful radiation doses.

Improvised Nuclear Device (IND) and Nuclear Weapon Detonation (NWD)

An improvised nuclear device (IND) can be described as a homemade atomic bomb in which the most likely configuration includes two subcritical masses of a fissile material that are quickly and forcefully brought together. Bringing these masses together allows for an uncontrolled fission reaction to occur, resulting in a massive release of energy in the form of thermal radiation, ionizing radiation, and a forceful pressure wave. Improvised nuclear devices are likely to cause more nuclear fallout because of incomplete fission due to a number of engineering complexities. They are also likely to be exploded at ground level rather than at an altitude, which causes ground materials to be irradiated and drawn up into the sky by the lifting of heated gases. Mistakes in the design and timing of the device may also result in a fizzle, where the criticality is too short-lived to consume all of the fuel or the device fails to achieve criticality, resulting in the fuel being dispersed without being consumed. The primary distinction between an IND and a traditional nuclear weapon is the sophistication of the manufactured device.

The nuclear weapons detonated over Japan during World War II were on the order of 10–15 kilotons (KT) of TNT and involved the use of only a few pounds of U-235 or Pu-238. Weapons developed later during the Cold War were on the order of megatons. When discussing nuclear weapons, it is important to realize that they are designed and manufactured

with very sophisticated nuclear, chemical, and electrical engineering skills and techniques. The detonation of a nuclear weapon would be devastating, with massive infrastructure damage and massive numbers of casualties. The fallout of radioactive material descending to the ground after being blown into the atmosphere by the detonation can result in significant radiation exposures. The acute and subacute consequences of such detonations will involve physical trauma and thermal burns, as well as radiation-induced illnesses/injuries.

Nuclear Power Plant (NPP) Incidents

NPP incidents are rare and historically have produced variable outcomes. Not all of these outcomes manifest physically. Sometimes the psychological or social impact can be equally devastating, and health effects may be more related to lack of daily necessities rather than radiation. The Chernobyl (1986) and Fukushima (2011) incidents resulted in multiple human health effects as a result of the incidents. Chernobyl resulted in 28 acute deaths from ARS, primarily related to exposures to, and contamination with, radioactive materials [2]. At Fukushima, the public health emergency from the Great East Japan Earthquake and tsunami resulted in many health effects and deaths; however, none of these were related to acute radiation effects. The Three Mile Island incident in 1976 also had no associated adverse human health effects from radiation. However, all incidents have had significant impact on psychological health and the environment.

Radiation-Induced Injuries and Illnesses

Internal Contamination

After a nuclear detonation or NPP incident, there may be radioactive fallout that can become widespread. This fallout may externally and internally contaminate (NPP only) both casualties and persons within the plume. External decontamination is accomplished through removing the contaminant by either wet or dry means, depending on the chemical composition. Internal contamination may be removed from the body or blocked to the organ of uptake. This should be done urgently, to avoid dose to organs/tissues. Knowledge of this for the oncologist is important as the internally contaminated patient may require therapy for a prolonged amount of time, i.e., after reaching definitive medical care. Following an R/N incident, consult the Radiation Emergency Assistance Center/Training Site by phone (24/7 emergency number, 865-576-1005) or access the REAC/TS RadMed Application, to assist with management of internal contamination with radioactive materials [3].

Acute Radiation Syndrome

Ionizing radiation has many mechanisms that induce injuries and illnesses. These mechanisms may cause direct or indirect injuries. For example, the energy from one ionization event is sufficient to directly break the chemical bonds of macromolecules, including DNA. Ionizing radiation generates free radicals, causing oxidation and oxidative stress, lipid peroxidation, and nitrosative stress, all indirectly injuring molecules and cells. The damage, indirect or direct, to DNA results in either single-strand or double-strand breaks, with the latter often misrejoining, leading to genetic changes including cell death. All of these processes, particularly in the more radiosensitive cells, will manifest as cellular, tissue, vascular, and, ultimately, organ damage. The noxious stimuli of radiation will cause nausea, protracted emesis, and, sometimes, fever as a prodrome. This usually lasts for ~ 48 h; however, higher acute exposures will have a shortened or absent prodrome.

As the dose of the exposure increases, the deterministic effects are seen in their classic syndrome, known as acute radiation syndrome (ARS). ARS is broken down into organ syndromes according to classic presentation at the organ's dose threshold. The earliest observations on the effect of acute radiation exposure on the various organs occurred after the atomic weapon detonations in Japan in August of 1945. In work starting in 1997, the Commission of the European Communities initiated a "Concerted Action" to give a scientific basis and synopsis for deciding the most appropriate medical interventions for ARS. Depending on radiation dose, clinical findings assigned to an organ system may occur concurrently or sequentially with those assigned to the other systems. The signs and symptoms of each of the resulting four organ syndromes of ARS (hematopoietic, gastrointestinal, cutaneous, and neurovascular) are summarized in tables below. The severity of signs and symptoms for each organ system is quantified as degrees of toxicity (degree 1, 2, 3, or 4). The response category (grade 1, 2, 3, or 4) correlates with overall severity of ARS and is determined by the highest degree of toxicity within any of the organ systems [4].

The hematopoietic syndrome (HS) shows classic expression with an acute, whole body (or a large portion of the body) exposure greater than 2 Gray (Gy). This is the identified triage decision point for US guidelines, though other countries use equal to or greater than 3 Gy. The mature lymphocytes are the most sensitive cell type to ionizing radiation. This makes this a helpful tool for triage. Most individuals will fully recover their bone marrow at the 2 Gy level. However, colony-stimulating factors (CSFs) are recommended to more quickly recover the bone marrow and avoid morbidity from infection. The classic HS is lymphopenia, followed by neutropenia, thrombocytopenia, and, eventually, pancytopenia with exposure to greater than 2 Gy.

The nadir of neutropenia is generally 3–4 weeks with a classic HS.

The gastrointestinal syndrome (GS) shows classic expression with an acute exposure to the whole/partial body, to include the torso, in the range of 6–8 Gy. The presentation is nausea, protracted emesis, diarrhea, gastrointestinal bleeding, bacterial translocation, and loss of absorptive capability of the intestines. Frank bowel necrosis may occur in the upper range of exposed dose. Acute renal dysfunction/failure may accompany GS.

The cutaneous syndrome (CS) classically begins expression with exposure to 6 Gy or higher. This syndrome presents with erythema, edema, desquamation, and, at higher doses, blistering, ulceration, and necrosis. At the dose threshold for deep ulceration and necrosis, these become complex and often non-healing or recurring wounds.

The neurovascular or cerebrovascular syndrome (NS) presents with acute exposure to doses of 10 Gy and up. This syndrome may present with nausea and protracted emesis within minutes, alteration of mental status or loss of consciousness, ataxia, high fever, fluid shifts and third spacing, seizures, cerebral edema, and coma (especially above 10 Gy). Neurovascular syndrome is not compatible with long-term survivability. Acute renal failure and pulmonary involvement may be concurrent. In acute doses in the 8–30 Gy range, pulmonary edema, pneumonitis, and fibrosis may occur.

Clinical Evaluation of Acute Radiation Injury

Clinical History and Laboratory

Proper application of a well-structured interview technique can contribute to an accurate diagnosis of radiation injury. Patients presenting with nausea, vomiting, and diarrhea may have many etiologies and may be misdiagnosed unless seen in conjunction with a known missing radiological source or incident. Evaluation of a patient suspected of a radiological exposure consists of a thorough event history, including geographic location at the time of the incident; how long the patient was in that location; was the patient sheltered and, if so, what kind of structure and location (basement, windows, etc.); if they exited the area, what pathway was taken and what form of transport was utilized; have they removed clothing/showered; did they have any signs of symptoms; a complete medical/surgical history; and a thorough physical examination. It would also be helpful to know if anyone else was co-located with them and, if so, if that individual is exhibiting similar signs and symptoms.

Laboratory evaluation should include a baseline and serial complete blood cell count with differential (CBC with diff) every 6–12 h to monitor for a decline in the absolute lymphocyte count. In papers by Goans et al., a simple prediction algorithm was presented to estimate effective whole-body dose within 8–12 h after moderate- and high-level gamma accidents and after criticality accidents [5–7]. The algorithm is based on the observation that lymphocyte depletion follows first-order kinetics after high-level gamma accidents. Using historical data from both gamma and criticality accidents, lymphocytes are observed to follow approximately an exponential decline in time within the first 24–48 h. This algorithm has been incorporated into the Armed Forces Radiobiology Research Institute (AFRRI) Biodosimetry Assessment Tool (BAT) program and the WinFrat tool [8] (Table 42.1).

Table 42.1 Absolute lymphocyte count decrease and approximate estimate of absorbed dose (R.E. Goans, personal data, 2014)

Absolute count 8–12 h post-event	*Rough estimate of absorbed dose*
1700–2500/mm^3	0–4 Gy
1200–1700/mm^3	4–8 Gy
<1000/mm^3	>8 Gy
Absolute lymphocyte count 48 h postexposure	*Absorbed dose estimate*
1000–1500/mm^3	1–2 Gy
500–1000/mm^3	2–4 Gy
100–500/mm^3	4–8 Gy
<100/mm^3	>8 Gy

A whole-body dose of 1 Gy or less should not noticeably depress the lymphocyte count below the normal range taken as 1500–3500/mm^3

An additional tube (green top, preferred lithium heparin) of blood should be collected for biodosimetry. This tube does not need refrigeration or centrifugation. This tube can be held for several days before being sent to the Radiation Emergency Assistance Center/Training Site (REAC/TS) Cytogenetic Biodosimetry Laboratory (CBL) for dicentric chromosome analysis (see Biodosimetry). A serum amylase may be helpful, as well as a C-reactive protein (CRP) which may be grossly elevated after a whole body exposure.

Blood typing and cross-match may be delayed unless needed for other medical/surgical indications. However, human leukocyte antigen (HLA) typing should be done immediately if the patient is a potential candidate for bone marrow transplantation (see National Network for Management of Mass Radiation Casualties), as it may take time to find a donor match.

Clinical Prodrome

Observation for any of the signs and symptoms of organ system involvement of ARS should be done for smaller incidents. In a mass casualty, patients presenting greater than 4–6 h after the incident who are symptom-free will be triaged as delayed and may follow up later with a community

reception center (CRC), private healthcare provider, or public health point of dispensing (POD). An early sign of significant, potentially non-survivable ARS is early, protracted emesis, not to be confused with a single episode from psychosomatic or sympathetic emesis. Anti-emetics, 5-HT3 receptor antagonists (ondansetron, granisetron), and dopamine antagonist (metoclopramide) are indicated for relief of emesis [4].

In work performed at Oak Ridge Associated Universities (ORAU) from 1964 to 1975, with patients undergoing long-term radiation therapy at a relatively low-dose rate ($n=502$ patients, 0.8–90 R/h), 50 percentile frequency doses were obtained as follows: ED50 = 1.08 Gy for anorexia, ED50 = 1.58 Gy for nausea, and ED50 = 2.40 Gy for emesis. A trend is noted whereby the time to emesis decreases with increasing dose [9, 10] though there is much variability among individuals and circumstances using this as a sole biodosimeter. The presence of early nausea, protracted emesis, diarrhea, and fever may correlate with the general range of exposure dose, approximately 100% of patients with whole-body dose greater than the LD50 or the dose required to cause mortality in 50% of the population (approximately 3.5–4.0 Gy without treatment) [11]. In addition, Hartmann et al. have noted an increased body temperature for effective whole-body dose >2.5 Gy and acute diarrhea for dose >9 Gy [12]. Other organ dysfunction clinical indicators that may be present up to 4 weeks or later after an terrorist or other incident include:

- Hematologic: lymphopenia, neutropenia, thrombocytopenia with resulting immunocompromise, petechial hemorrhages, and/or mucosal bleeding
- Gastrointestinal: emesis, diarrhea with or without bleeding, fluid loss with dehydration, subsequent renal dysfunction, and potential cardiovascular dysfunction
- Neurovascular or cerebrovascular: mental status changes, cerebral edema, possible seizures, and coma

Cytogenetic Biodosimetry

Since 1963, the dicentric chromosome assay (DCA) has been extensively developed, researched, and validated in numerous incidents to be the global gold standard for biodosimetry [13]. Researchers at AFRRI and REAC/TS have established the conventional lymphocyte metaphase-spread dicentric assay and have applied it to the clinical management of several overexposure incidents. The DCA is radiation-specific, is sensitive as low as 0.2 Gy, and is not affected by ethnicity or gender. REAC/TS is automating much of the process, and Columbia University has a completely automated system to perform the DCA. One of the limitations of DCA is that it is not available as a point-of-care (POC) test and may take several days for results. Another limitation is the upper end of dose assessment is approximately 5 Gy. Techniques such as premature chromosome condensation (PCC) assay are a good addition to DCA in extending the dose range above the NS syndrome.

Recently, it was suggested that the dicentric assay may be adapted for the triage of mass casualties [14–16]. Lloyd et al. described an in vivo simulation of an accident with mass casualties receiving whole- or partial-body irradiation in the 0–8 Gy range [14]. Faced with an urgent need for rapid results, clinical triage was accomplished by scoring as low as 20 metaphase spreads per subject, compared with the typical 500–1000 spreads scored in routine analyses for estimating dose. However, Lloyd et al. suggested increasing the analyses to 50 metaphase spreads when there is disagreement with the initial assessment or when there is evidence of significant inhomogeneous exposure [14, 17] (Table 42.2).

There are other biodosimetric techniques being researched with point-of-care testing potential. Many of these look for metabolomics and show promise for the future.

Table 42.2 Proposed biodosimetry technique as a function of expected dose

Dose range (Gy)	Proposed validated dosimetry method	Prodromal effects	Manifest symptoms	Survival expectancy
0.1–1	Dicentric/PCC	None to mild (1–48 h)	None to slight decrease in blood count	Almost certain
1.0–3.5	Lymphocyte depletion kinetics/ dicentrics/PCC	Mild to moderate (1–48 h)	Mild to severe bone marrow damage	0–10% death
3.5–7.5	Lymphocyte depletion kinetics/PCC	Severe (1–48 h)	Pancytopenia, mild to moderate GI damage	10–100% death within 2–6 weeks
7.5–10.0	Lymphocyte depletion kinetics/PCC	Severe (<1–48 h)	Combined BM and GI damage	90–100% death within 1–3 weeks
>10.0	PCC	Severe (minutes to <48 h)	GI, neurological, cardiovascular damage	100% death (within 2–12 days)

From Prasanna et al. with permission [17]
PCC premature chromosome concentration

Acute Radiation Syndrome (ARS)

The timing and severity of ARS depend upon the radiation quality, dose, dose rate, and irradiated area(s) (organs). Clinical findings associated with an organ system may occur concurrently or sequentially with those assigned to the other systems.

Hematopoietic Syndrome (HS)

Hematopoietic stem/progenitor cells in the bone marrow and circulation are particularly sensitive to ionizing radiation with a dose (D0) of approximately 1 Gy at a dose rate of 0.8 Gy/min [18] (Table 42.3). At doses of 2–3 Gy, hematopoietic stem/progenitor cells exhibit reduced capacity to divide. Morphological changes in interphase cells of the bone marrow include nuclear karyorrhexis, cytoplasmic fragments, nuclear and intercellular bridging, multinuclearity, and pseudo-Pelger-Huet anomaly [19, 20]. Chromosomal bridges and fragments are seen in actively dividing cells of the marrow. Bone marrow hypoplasia and/or aplasia may develop at doses >5–7 Gy, resulting in severe pancytopenia weeks to months after exposure [21]. The pathophysiologic mechanisms underlying these radiation-induced effects on the bone marrow involve dose-dependent and clonal elimination of stem/progenitor cell populations and their progeny [22, 23]. Various degrees of pancytopenia develop several weeks after exposure and need serial CBC and differential every 12–24 hours, as opposed to the more frequent monitoring of the early lymphopenia in the first 24–48 hours post incident [24, 25].

Table 42.3 Hematopoietic syndrome modified from Fliedner, et al. [4]

	Degree 1	Degree 2	Degree 3	Degree 4
	Mild damage	Moderate damage	Severe damage	Fatal damage
Hematopoietic system				
Lymphocyte count[a]	At/above **1.5** × 10^9 cells/L	**1.0–1.5** × 10^9 cells/L	**0.5–1.0** × 10^9 cells/L	Below **0.5** × 10^9 cells/L
Granulocyte count[b]	At or above **2** × 10^9 cells/L	**1–2** × 10^9 cells/L	**0.5–1.0** × 10^9 cells/L	Below **0.5** × 10^9 cells/L
Thrombocyte count[c]	At or above **100** × 10^9 cells/L	**50–100** × 10^9 cells/L	**20–50** × 10^9 cells/L	Below **20** × 10^9 cells/L
Hemoglobin	Normal	Decreases 0–9%	Decreases 10–20%	Decreases more than 20%

Note: Reference values will vary by laboratory
Values are in SI units
10^9/L = 10^9 cells/L = 10^3 cells/μL = 10^3 cells/mm^3 (cubic millimeter)
[a]Reference value: (1.5–4) × 10^9 cells/L
[b]Reference value: (4–9) × 10^9 cells/L
[c]Reference value: (140–400) × 10^9cells/L

Lymphocytes are the most radiosensitive of the circulating blood cells in spite of their being terminally differentiated and largely mitotically inactive. Radiation may alter recirculation properties and surface antigen expression of lymphocytes [4, 26]. The rate of decline in lymphocytes is directly dependent on the absorbed radiation dose.

Other hematological findings include a decline in the absolute neutrophil count (ANC) and the platelet count. The ANC may briefly increase within hours after exposure, a phenomenon first described by Fliedner as an abortive rise [4]. The abortive rise is believed to be due to migration of preformed myeloid elements across the marrow-blood barrier into the circulation, although demargination cannot be excluded as a mechanism for this transient effect. Thereafter, the ANC declines over several days to weeks, depending on radiation dose. The abortive rise is typically seen with HS-1 and HS-2 and appears to indicate reversible marrow damage from a survivable exposure. The absence of an abortive rise in ANC is observed in HS-3 and HS-4 and appears to indicate irreversible bone marrow damage. Neutropenia and thrombocytopenia reach a nadir at 1–2 weeks after exposure to >3–4 Gy. Anemia follows due to impaired erythropoiesis and severe bleeding may occur secondary to thrombocytopenia.

The most significant consequences of lymphopenia and neutropenia are disruption of immune defenses and predisposition to life-threatening infections. ANCs of <500–1000 cells/mm^3 (HS-3 and HS-4) are associated with bacterial, viral, and fungal infections, similar to what occurs in the setting of neutropenia and lymphopenia from any other cause. Management of febrile neutropenia should follow guidelines recommended by the Infectious Diseases Society of America (IDSA), using broad-spectrum prophylactic and therapeutic antimicrobial agents [27].

Managing HS includes administration of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) when the dose is expected to be >2 Gy and/or when it is anticipated that the ANC will decline to <500 cells/mm^3 for 7 days or longer [28]. The Food and Drug Administration (FDA) has approved these myeloid colony-stimulating factors for use in a radiological incident. Initiate CSF therapy within 24 h of exposure and continue until the ANC reaches and maintains a level of >1000 cells/mm^3 in the absence of active infection. For individuals with active infection, continue cytokines together with antimicrobial agents, according to guidelines of the IDSA [27].

Erythroid-stimulating agents (ESAs) may be used as clinically indicated [28]. The rationale for ESA therapy is avoiding need for red blood cell infusion. The lowest dosage that induces a hemoglobin level of >9–10 g/dL is appropriate. Iron supplementation may also be used in conjunction with ESA therapy.

Other growth factors, including stem cell factor, interleukin-3, and the pegylated form of erythropoietin and G-CSF, have been administered sequentially or concomitantly with G-CSF and/or GM-CSF to victims of a radiological incident [28]. These growth factors and new thrombopoietic factors may be useful as in aplastic anemia; however, there is no evidence-based recommendation at this time [29].

Because radiation injury to the bone marrow is typically heterogeneous, leaving areas of unirradiated or minimally irradiated/damaged marrow that are capable of reconstituting lymphohematopoiesis over time, a watch-and-wait approach is recommended after initiating myeloid growth factor therapy. Administration of hematopoietic stem cells (HSCs) should be considered only after failure of a 2–3-week trial of cytokine treatment has been demonstrated [28]. A review of 31 patients undergoing HSC transplantation for accidental radiation injury found that 27 patients died and the remaining 4 patients survived with a rejected allograft [30]. Causes of death after therapeutic HSC transplantation include burns (55%), hemorrhage (41%), infection (15%), and acute respiratory distress syndrome (ARDS) (15%) [31]. Since survival outcomes are poor among HSC transplant recipients with radiation burns, GS, renal failure, and/or adult ARDS, HSC transplantation should not be performed in individuals with non-hematopoietic organ failure and/or active infection [28, 32]. In the case of a large radiological incident, the Radiation Injury Treatment Network (RITN), a voluntary consortium consisting of >70 transplant centers, donor centers, and umbilical cord blood banks, will be activated (see National Network for Management of Mass Radiation Casualties) [33, 34].

When transfusion is indicated for severe cytopenia, blood products should be irradiated (25 Gy) to prevent transfusion-associated graft-versus-host disease (TA-GVHD). Since TA-GVHD is almost universally fatal in this population, its prevention by prior irradiation of blood products is mandatory. Leukoreduction may lessen febrile reactions and the immunosuppressive effects of blood transfusion, limit platelet alloimmunization, and reduce CMV infection [35, 36]. Leukoreduction is recommended whenever feasible.

National Network for Management of Mass Radiation Casualties

In the USA, a network has been developed that includes transplant centers, hospitals, blood donation centers, and stem cell banks to provide resource-intense medical management of mass casualties from a radiological event. The Radiation Injury Treatment Network (RITN) provides comprehensive evaluation and treatment for victims of radiation exposure or other marrow toxic injuries (like those caused by mustard agent). Many of the casualties with radiation injury will be salvageable but require specialized outpatient and/or inpatient care. Recognizing this need, the US National Marrow Donor Program/Be The Match Marrow Registry, the US Navy, and the American Society for Transplantation and Cellular Therapy (formerly known as American Society for Blood and Marrow Transplantation) collaboratively organized RITN, which provides expertise in the management of bone marrow failure, blood component therapy, stem cell collection, and umbilical cord blood banking around the globe.

The RITN is preparing for the resulting medical surge of radiation casualties from the detonation of an improvised nuclear device.

The goals of RITN are:

- To develop treatment guidelines for managing hematologic toxicity among victims of radiation exposure
- To educate healthcare professionals about pertinent aspects of radiation exposure management through training and exercises
- To help coordinate the medical response to radiation events
- To provide comprehensive evaluation and treatment for victims at participating centers

The RITN collaborates with the Department of Health and Human Services-Assistant Secretary for Preparedness and Response to ensure coordination following a mass casualty marrow toxic incident that would require their involvement in a national response. The RITN has developed ARS Treatment Guidelines, Referral Guidelines, as well as web-based training materials for hospitals that receive individuals who show early signs of ARS [37]. In addition, the RITN regularly collaborates with organizations to expand the availability of treatment materials. Through a collaboration with Epic Software Systems, RITN developed Adult and Pediatric Medical Order Sets to be available through the Epic electronic health record system for any hospital that utilizes the system. In collaboration with staff managing the Radiation Emergency Medical Management (REMM) website, RITN developed treatment orders for adults and children [38], and RITN has ongoing efforts with the American Burn Association to formalize combined practice guidelines to meet the needs of caring for patients with combined injuries of trauma and radiation.

The RITN estimates that, of survivors from an IND detonation, only 1% of radiation casualties will be candidates for hematopoietic stem cell transplantation. Approximately 30% of casualties are expected to require specialized supportive care in an inpatient setting that involves isolation to protect individuals with febrile neutropenia. Finally, nearly 70% of casualties are expected to require ambulatory care for treatments such as administration of cytokines and antimicrobials, serial assessment of the CBC, and calculation of the absolute lymphocyte count [37].

RITN medical staff are specialists in hematology and oncologic who have daily experience in treating patients with hematologic signs and symptoms that characterize HS. Hospitals that participate in RITN have established standard operating procedures (SOPs) for managing mass casualties. They coordinate locally with emergency management personnel and public health officials and conduct annual training and exercises to constantly improve their level of preparedness.

Cutaneous Subsyndrome (CS)

Injury to the skin and subcutaneous tissues is highly dependent on localized radiation dose [39–41] (Table 42.4). The external dose thresholds at which the deterministic effect manifest begin at 6 Gy with erythema. A transient epilation may occur at Gy but permanent epilation occurs around the Gy threshold. Desquamation, both dry and moist, will occur at ranges of 10–15 and 15–20 Gy, respectively. At doses greater than 25 Gy, ulceration of deeper tissues and necrosis may occur. Prodromal pain, erythema, and edema may occur for 24–48 h. At higher doses, the prodrome will be shorter or absent. The damage to subcutaneous tissues is highly dependent upon the type and energy of the radiation, as well as the duration of irradiation. These wounds will differ from thermal burns in the pathophysiology. The repeated release of proinflammatory mediators will result in a wound that evolves over weeks, months, or even years. The complex wounds seen at necrosis threshold ranges will often heal with repeated recurrence or not heal completely, often resulting in surgeries and possible amputation. It is important for the hematologist-oncologist to recognize that, when the involved total body surface area is greater than 40%, these may cause great morbidity and mortality. Of the 28 acute deaths in the Chernobyl incident, the primary cause of death for 16 of these patients was CS, according to Gottlöber et al. [42]. It is of extreme importance to realize that these cutaneous syndromes and complex wounds may not fully manifest for 3–4 weeks after an incident, after arrival to a definitive care treatment facility.

Managing CS includes topicals: Class II and III steroids, antihistamines, and antibiotics [4, 43]. The REAC/TS past and present experience has found that hyperbaric oxygen therapy, pentoxifylline with topical and/or oral alpha-tocopherol, and artificial skin constructs are helpful. Newer silver-based treatments should be considered. Systemic steroids should be decided on a case-by-case basis. Surgical debridement, wide local excision, skin grafts/flaps, or amputation may be necessary [44]. Newer techniques, mesenchymal stem cell [45, 46] or adipose-derived stromal vascular fraction injections [47], with or without surgery, may lead to more long-term healing and relief from intractable pain from compression of cutaneous nerve bundles. Clinical trials using these techniques with thermal burns are underway in the USA. Other countries have both bench research and clinical trials with these therapies; however, lack long-term follow-up is still necessary [45–48].

Gastrointestinal Subsyndrome (GS)

The rapid turnover of the extremely radiosensitive epithelial cells lining the gastrointestinal tract demands that the stem cells in the crypts of Lieberkuhn are functional. The hematologist-oncologist is certainly familiar with the noxious stimuli of various chemotherapy and radiotherapy regimens inducing nausea, anorexia, and, possibly, protracted emesis. This is similar to the prodrome seen with ARS. If nausea and emesis occur within the first hour of exposure and, if accompanied by diarrhea, is likely from both central and peripheral nervous system and is indicative of a potentially non-survivable dose [4]. At doses of 5–6 Gy or greater, damage occurs to stem cells in the crypts, leaving the lining of the gastrointestinal (GI) tract denuded [24, 25]. These findings may be accompanied over time by hematemesis,

Table 42.4 Cutaneous syndrome modified from Fliedner, et al. [4]

	Degree 1	Degree 2	Degree 3	Degree 4
Symptom or sign	Mild damage	Moderate damage	Severe damage	Critical/fatal damage
Cutaneous system				
Erythema[a]	Minimal; transient	Isolated patches 0–9% TBSA[b]	Marked erythema, may have some confluence 10–40% TBSA	Severe; may have confluence >40% TBSA
Pain	None, may have pruritus	Slight	Moderate and persistent	Severe and intractable pain
Blistering and desquamation	Rare, sterile fluid	Rare blister; dry desquamation	Bullae; moist desquamation	Bullae with bleeding; moist desquamation
Deep ulceration/ necrosis		Dermal	Subcutaneous tissue	Muscle, organ, or bone involvement

[a]Extent of the TBSA is decisive
[b]*TBSA* total body surface area

hematochezia, frank bloody emesis or diarrhea, fluid and electrolyte shifts, hypovolemia with eventual renal failure, and cardiovascular collapse (Table 42.5).

Sloughing of the lining of the GI tract removes the barrier to bacterial translocation from the intestinal lumen to the bloodstream. Bacterial translocation occurs at a time of immunocompromise from neutropenia and lymphopenia, predisposing to sepsis [49].

Managing GS includes antimicrobial prophylaxis and therapy to achieve therapeutic drug levels (rather than bowel decontamination), replacement of fluids and electrolytes, loperamide, and a serotonin receptor antagonist to control emesis [4, 43].

Neurovascular Subsyndrome (NS)

Neurovascular syndrome (NS), characterized by acute, irreversible neurotoxicity, occurs at whole-body doses of >10 Gy (Table 42.6). Abnormalities in EEG may occur after low doses of radiation, and a milder NS may occur at 3–4 Gy, with mild headache, limited emesis, and hypotension. The prodrome begins as noxious stimuli gain access to blood and cerebrospinal fluid and may result in anorexia, nausea, and emesis. The signs and symptoms of moderate- to high-dose exposure include mental status changes, fatigue, dizziness, hypotension, syncope ataxia, seizures, and coma. Managing NS includes serotonin receptor antagonists, mannitol, furosemide, anti-seizure medications, and analgesics [4, 43]. In a mass casualty, resource-scarce setting, these patients would initially be put in an expectant category. Comfort or hospice care should be provided for these patients.

Other Considerations

Involvement of the tracheobronchial tree and lungs is observed at 1–6 months following exposure to a high radiation dose [50]. Edema and leukocyte infiltration of the lung parenchyma occur during the initial day to week after exposure. An acute exudate occurs after 1–3 months, followed by collagen deposition and fibrosis after months to years. Pulmonary edema and acute respiratory distress syndrome (ARDS) may be delayed and seen after high doses [4]. Interstitial pneumonitis accompanied by a restrictive ventilatory defect may lead to death. Management of respiratory failure includes ventilatory support with a lung protection strategy, using the lowest possible inhaled oxygen concentration to maintain an arterial oxygen saturation of >90% [43]. Radiation damage may occur in other organ systems, including the renal, vascular, and cardiac systems. Multiorgan failure (MOF) can be an intermediate- to long-term complication of radiation exposure with significant morbidity and mortality [51, 52]. Vigilance for damage to other organ systems must be maintained throughout medical care.

Table 42.5 Gastrointestinal syndrome modified from Fliedner, et al. [4]

	Degree 1	Degree 2	Degree 3	Degree 4
Symptom or sign	Mild damage	Mild-moderate damage	Severe damage	Serious/fatal damage
Gastrointestinal system				
Diarrhea				
Frequency/ bleeding	2–3 stools/d; occult blood	4–6 stools/d; some blood	7–9 stools/d; bloody	Refractory, watery diarrhea; "gross hemorrhage"
Mucosal loss/day	Intermittent	Large and intermittent	Persistent	Large, persistent

Table 42.6 Neurovascular syndrome modified from Fliedner, et al. [4]

	Degree 1	Degree 2	Degree 3	Degree 4
Symptom or sign	Mild damage	Moderate damage	Severe damage	Fatal damage
Neurovascular system				
Vomiting	Occasional	Intermittent	Persistent	Refractory
Temperature °F/°C	<100.4/38	100.4–104/38–40	>104/40 <24 h	>104/40 >24 h
Hypotension (mm/Hg)	~ normal >100/70	<100/70	<90/60	<80/
Fatigue/ neurologic deficit[a]	Performs activities	Interferes with work/performs activities with noticeable deficit	Assistance for daily activities/cannot perform normal activities; prominent deficit	No activities/loss of consciousness; "life-threatening" neurologic signs
Cognitive deficits	Minor	Moderate	Major impairment since exposure	Complete impairment

[a]Neurological deficits: Reflex status including reflexes of the eye, ophthalmoscopy (edema of papilla), fainting, dizziness, ataxia, and other motor signs and sensory signs

Summary

A myriad of specialists, especially those well versed in hematologic abnormalities, will be required for any significant ionizing radiation injury to the whole body, or a significant portion thereof, because of the potential for injury to circulating WBCs or the bone marrow. In fact, inappropriate management of the HS will almost certainly result in elevated morbidity, if not mortality, from the HS itself or damage to other organ systems. The manifestations of immunologic incompetence, including the spectrum of infectious diseases, must be treated properly in order to improve patient survival. Practitioners must be also vigilant for multiple organ dysfunction/failure secondary to ionizing radiation exposure.

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Delirium

43

Zahra Alhajji and Ahmed Elsayem

Case Study

A 65-year-old woman with advanced uterine cancer presented to the emergency department (ED) with increasing abdominal pain, lethargy, and insomnia. She received her last round of chemotherapy treatment 5 days earlier and takes morphine 15 mg every 4 hours as needed for pain. She had taken the maximum dose for the previous 3 days and was unable to sleep because of increasing pain and anxiety. Her son stated that she was unable to eat or drink (except when taking her pain medication) because of drowsiness. Physical examination demonstrated a chronically ill-appearing patient with dehydration and cachexia. Her abdomen was soft, with generalized tenderness and no rigidity. She was easily arousable and, when asked, reported pain intensity of 10 out of 10. She was tachycardic, but other vital signs were normal. Her son, who was exhausted, left her in the ED and went home. Initial laboratory tests revealed a high blood urea nitrogen level. Intravenous hydration was initiated, and the patient received intravenous morphine 4 mg every hour as needed for severe pain. Shortly after, the patient was taken to radiology for abdominal and head computed tomography. She became agitated, pulled on her IV lines, and began bleeding. She hit the radiology technician, and the ED was notified. The patient was given lorazepam IV to control her agitation, and a 24-hour sitter was ordered. The patient was admitted to the hospital, and palliative care was consulted. Pain medications were changed to fentanyl, and haloperidol was ordered for agitation. Further evaluation revealed cancer progression. A family meeting was held, and the patient was discharged to hospice care.

Introduction

Delirium is a common neuropsychiatric syndrome among patients with cancer, particularly in elderly patients, those receiving opioids, and those with advanced disease. Over 80% of patients with advanced cancer will develop delirium in the last hours and days before death. Approximately 50% of episodes are reversible [1]. Delirium is a predictor of short survival and is a significant cause of distress among patients, family members, and healthcare providers [2, 3].

Definitions

Terms used in relation to delirium may be imprecise and nonspecific. We will use the following definitions:

- Altered mental status (AMS): A broad term encompasses all manifestations of brain dysfunction, including confusion, clouding of consciousness, disorientation, inattention, altered behavior, or drowsiness [4].
- Confusion: The quality or state of being bewildered or unclear. Confusion is usually a symptom of delirium or dementia [5].
- Delirium: A more specific term commonly used to describe an acute state of confusion resulting from organic brain dysfunction. Delirium is characterized by an acute onset of fluctuating levels of consciousness and severe disturbance of mental abilities which results in confused thinking and reduced awareness of the environment [5–8].

Epidemiology

The exact prevalence of delirium in ED patients with advanced cancer is unknown. We found a frequency of 9% among patients with advanced cancer presenting to the MD Anderson Cancer Center ED [9]. The literature supports rates of 8% to 17% among all elderly patients seen in general EDs

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[10–12]. Among emergently transferred and hospitalized nursing-home elderly, 38% will develop delirium [12]. The highest rates of delirium are seen near the end of life; in one study, 88% of patients with advanced cancer treated in an inpatient palliative care unit experienced terminal delirium. Among hospitalized patients with cognitive impairment, such as dementia, almost half will develop delirium [13]. Siddiqi et al. conducted a systematic review of 42 cohorts and found the prevalence of delirium at admission ranged from 10% to 31%, with the incidence per admission ranging from 3% to 29% and occurrence rates per admission from 11% to 42% [14]. In another systematic review, Gibb et al. reported a delirium frequency of 23% in hospitalized patients [15].

Delirium is even more prevalent among patients with advanced cancer, particularly patients receiving palliative care [16, 17]. In a systematic review of 42 studies, Wattet et al. reported a prevalence ranging from 44% to 88% across all palliative care settings [16]. Fann et al. reported a 50% cumulative incidence of delirium over 30 days following hematopoietic stem cell transplant [18].

Etiology and Pathophysiology

The precise cause of delirium is unknown, but the syndrome tends to occur in predisposed individuals who have underlying comorbid conditions and experience additional insults [1, 19, 20]. Evidence suggests that delirium is a multifactorial condition resulting from structural or nonstructural brain pathology.

Doriathet et al. reported that toxic metabolic factors (frequently multifactorial) are the most common causes of delirium [21]. The most common contributing factors are medications, infection, electrolyte abnormalities, renal insufficiency, liver dysfunction, anticancer drugs, infections, and opioids [22–24].

Tuma and DeAngelis reported that the causes of delirium were multiple in about two-thirds of cases. Only 15% had structural lesions as a cause of AMS [25]. Doriathet et al. studied 100 consecutive patients with confusion, finding that 36% were due to structural causes [21]. Other overlooked but important factors are loneliness and unfamiliar environments, which add to the psychological stress afflicting cancer patients. Given the complex nature of delirium and its multifactorial etiologies, it is difficult to subsume delirium under one heading.

Table 43.1 lists conditions that can cause or contribute to delirium. Medications, particularly opioids, are a frequent proximal cause of delirium in patients with advanced cancer [26, 27]. Table 43.2 lists medications that can contribute to delirium.

Neurotoxicity is a known complication of chronic opioid therapy and may be manifested by delirium, hallucinations (particularly visual hallucinations), myoclonus, and hyperalgesia. Chronic high-dose opioid therapy and coadministration of opioids and other psychoactive drugs, such as benzodiazepines, are common predisposing factors for delirium. Opioid-induced neurotoxicity is believed to be caused by opioid end products, such as morphine-3-glucuronide (in the case of morphine) [23, 28, 29]. The majority of opioids have similar active metabolites. These opioid metabolites are usually excreted by the kidneys and accumulate with renal insufficiency; therefore, dehydration and acute or chronic renal failure may decrease their clearance.

Opioids may exert their toxic effects via the cholinergic system [23]. Central neurotransmitter disturbances are believed to be the final common pathophysiologic mechanism causing delirium. Most of these theories, reviewed by Maldonado, center on neurotransmitter roles, inflammatory cytokines, and blood-brain barrier integrity in delirium development. The neurotransmitter hypothesis

Table 43.1 Common conditions that could contribute to delirium

Conditions that contribute to delirium	Examples
Medications	Mainly opioids, benzodiazepines, steroids, some antiemetics, certain chemotherapies
Infection	Urinary tract infection, pneumonia, sepsis
Organ failure	Renal, hepatic, pulmonary, cardiac
Primary CNS insult	Primary or metastatic brain tumors, cerebrovascular accidents, leptomeningeal disease
Withdrawal from medications	Alcohol, benzodiazepines
Electrolyte imbalance	Hyponatremia, hypercalcemia
Metabolic/endocrine	Hypothyroidism, paraneoplastic syndrome,
Others	Uncontrolled pain, dehydration, malnutrition, change in environment/ stimulation

Table 43.2 Common medications that could contribute to delirium

Medication category	Examples
Opioids analgesia	Morphine, hydromorphone, oxycodone, fentanyl
Antiemetics	Prochlorperazine, promethazine
Antibiotics	Fluoroquinolones; gemifloxacin, levofloxacin, moxifloxacin
Antivirals	Acyclovir
Sedatives	Benzodiazepines; lorazepam, diazepam, midazolam
Muscle relaxants	Baclofen,
Antihistamines	Diphenhydramine, dimenhydrinate, hydroxyzine
Antidepressants and mood stabilizer	TCAs, SSRIs, lithium
Cardiac medications	Antiarrhythmics, digitalis
Chemotherapy	Ifosfamide, 5-fluorouracil, paclitaxel, vincristine, cisplatin, cytosine arabinoside

TCA tricyclic antidepressant, *SSRI* selective serotonin reuptake inhibitor

builds upon the role of neurotransmitter changes in the development and treatment of delirium and AMS.

Other neurotransmitter abnormalities that may contribute to delirium include excess serotonin and cortisol levels, as well as reductions in GABA (γ-aminobutyric acid) levels [30]. More recently, increasing attention has been given to the role of cytokines, such as interleukins 1 and 6, tumor necrosis factor, and pro-inflammatory markers, such as C-reactive protein, in causing delirium. These are consistent with the neuro-inflammatory hypothesis, which implies that peripheral inflammation results in the activation of CNS parenchymal cells, which produces inflammatory cytokines that alter the normal functioning of neuronal synapses. This hypothesis could explain the "sickness behavior" seen in patients with inflammation or infections [31, 32].

Clinical Personation and Diagnosis

Three clinical subtypes of delirium have been described, classified by the patient's psychomotor activity and arousal level [33]:

- Hyperactive: confusion + agitation ± hallucinations ± delusions ± myoclonus ± hyperalgesia. The patient may fidget around the room, attempt to pull out lines, repeat movements and names, etc. Its features mimic those seen in psychosis, mania, or extrapyramidal side effects of medications.
- Hypoactive: confusion + somnolence ± withdrawal. Usually manifests with withdrawal, psychomotor retardation or lack of movement, lack of orientation, paucity of speech, and unresponsiveness. This type of delirium may mimic a depressed mood.
- Mixed: alternating symptoms of both hyperactive and hypoactive delirium. This form is the most common in advanced cancer patients.

The gold standard for diagnosing delirium is psychiatric evaluation based on criteria set forth by the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). Based on these criteria, diagnosing delirium will require all of the following [34, 35]:

A. A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
D. The disturbances in Criteria A and C are not explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin or is due to multiple etiologies.

Patient Evaluation

The clinician should maintain a high index of suspicion and look for clues within the patient's presentation, such as new-onset agitation that peaks at night or variations in sleep patterns (generally sundowning) in which patients sleep during the day and remain awake at night. Also, patients will have memory deficit and difficulty mentioning names of people and places. Relatively acute onset of symptoms with a fluctuating pattern helps distinguish delirium from more chronic conditions such as dementia, which occurs gradually over months and years. Ask the patient specifically about hallucinations (they are more often tactile than visual) and delusional thoughts. Look for clinical signs of sepsis, opioid toxicity, dehydration, metabolic abnormalities, or other potential causes of delirium. Family members or other surrogates may provide valuable information such as changes in cognition, memory, or behaviors. Inattention is a vital finding to observe while assessing delirious patients.

Screening Tools

Multiple tools have been developed in order to facilitate the detection of delirium. Most of these tools used for screening and diagnosis of delirium are based on the DSM criteria. LaMantia conducted a systematic review and concluded that although several tools were used in the ED, only one was validated and, because of limited information, there are no specific recommendations for screening of delirium in ED [36].

The CAM (Confusion Assessment Method) is the most validated screening tool for delirium in the ED [37]. The CAM for the Intensive Care Unit (CAM-ICU) has also been evaluated as an ED screening tool with good reported accuracy [38–40]. In a systematic review, Mariz et al. [41] suggest that the CAM-ICU has potential to be the reference for diagnosing delirium in ED. The Single Question in Delirium is an easy and quick tool to screen for delirium [42].

Table 43.3 lists some commonly used screening and diagnostic tools. Some patients with delirium may appear cog-

Table 43.3 Delirium screening and diagnostic tools

Tool	Purpose	Main Features
Nu-DESC [43]	Screening	Used by nurses at the bedside Brief (5 items, requires <2 min)
MMSE [32]	Screening	Test of cognitive failure 30 items (score <24 signifies greater cognitive failure) Commonly used for dementia but may be used as a screening tool for delirium
CAM [37]	Screening and diagnostic	Based on DSM-III-R [34] criteria Brief (four features, could be completed in <5 min) Simple, but users need training Does not rate the severity
Single Question in Delirium [42]	Screening	Simple and brief Easy to administer
MDAS [44]	Severity rating	Differentiates among subtypes of delirium Easy to administer by a non-medically trained person Ten items, 30-point scale (higher scores signify greater severity) Some groups use cutoff score >7 to diagnose delirium [44]
CAM-ICU [40]	Diagnosis in ICU, screening in ED	Based on CAM Originally validated to assess delirium in ICU Evaluated in ED setting

Nu-DESC Nursing Delirium Screening Scale, *MMSE* Mini-Mental State Examination, *CAM* Confusion Assessment Method, *DSM-III-R* Diagnostic and Statistical Manual of Mental Disorders, Third Edition–Revised, *ED* emergency department, *MDAS* Memorial Delirium Assessment Scale, *CAM-ICU* Confusion Assessment Method for the Intensive Care Unit

nitively normal and follow commands appropriately; thus, using a screening tool can provide valuable guidance toward an accurate diagnosis of the condition. Because of time constraints in the ED, a shorter screening tool may be more practical [43]. The single question delirium screen is a short and practical ED screening tool when answered by the patient and surrogate [34]. However, further research is needed to evaluate its utility. The Memorial Delirium Assessment Scale (MDAS) is easy to administer by a lay-trained person, but it is time-consuming [44]. The MDAS may be more sensitive than CAM in diagnosing ED delirium [45].

Diagnosing delirium superimposed on dementia is challenging. Family identification of delirium using CAM instrument (FAM-CAM) is an informant-based delirium assessment that may help overcome the barriers to delirium screening in patients with dementia [46]. The FAM-CAM consists of 11 items that characterize changes in attention, speech, arousal, and orientation; a patient's family member or caregiver who knows the patient's baseline mental and cognitive status well completes it. To improve delirium recognition in the ED, however, we must move beyond just conducting research and take a more active approach to diagnosing delirium while incorporating implementation science principles.

Differential Diagnosis

Depression and dementia may complicate the differential diagnosis of delirium, and hypoactive delirium may be misdiagnosed as depression, with resultant inappropriate treatment. Agitated delirium may be wrongly assessed as anxiety, insomnia, or psychosis and treated with benzodiazepines. The presence of grimacing or moaning may be interpreted as inadequate pain resulting in inappropriately opioid dosing. Urinary retention and constipation can aggravate agitation. Previously unrecognized cognitive dysfunction may manifest itself as delirium during cancer treatment. Patients may have episodic lucid intervals marked by the clearing of their sensorium.

Management

Step 1. Assessing the Patient

Maintain a high index of suspicion. Ask family members or the nurse caring for the patient about new symptoms, especially symptoms at night.

Use a screening tool such as CAM, MDAS, Clock-making, or Mini-Mental State Examination (identifies cognitive impairment only). These screening tools should be used even in patients with no overt signs of delirium to make an early diagnosis. Ask specifically about hallucinations (they are more often tactile than visual) and delusional thoughts. Look for clinical signs of sepsis, opioid toxicity, dehydration, metabolic abnormalities, or other potential delirium causes [47, 48].

Order appropriate laboratory tests early, such as a complete blood count, electrolytes, calcium (with albumin), and renal and liver function. Imaging tests that may help include chest x-ray, brain CT/MRI, and O2 saturation, with other tests ordered as clinically indicated.

Step 2. Reviewing the Environment

- Ensure a physically safe environment and minimize noise and excessive light.
- Provide the presence of familiar objects and a visible clock and calendar.
- Include the family by asking them to assist with reorientation.
- Pain levels and the patient's need to use the bathroom should be addressed.

- The bed should be lowered to minimize fall-related injury.
- The patient and surrogate should be advised to call the nurse if the patient wants to leave the bed for any reason, including going to the restroom.
- If no caregiver is available, a sitter should be assigned to assist the patient; however, a familiar face is preferable to a stranger [49, 50].
- Use of restraints or any tethering agent, such as Foley catheters, ECG leads, and oxygen saturation or blood pressure monitor lines, is discouraged. These items may worsen agitation in the delirious patient. Familiar items such as photographs of family members may help calm the patient [47, 51–53].

Step 3. Treating the Symptoms of Delirium

Agitation and Hallucinations Haloperidol is the drug of the first choice. Treatment can be started with haloperidol 0.5 = 1 mg PO/SC/IV q6h and 1–2 mg PO/SC/IV q2h as needed. To bring severe agitation rapidly under control, it may be necessary to give haloperidol more frequently initially (e.g., 1–2 mg q30 min SC/IV as needed during the first hour and q1h prn after that).

The oral bioavailability of haloperidol is approximately 60–70%, and this should be taken into account when converting from the oral to the parenteral route and vice versa. It is essential to bring agitated delirium under control as rapidly as possible to prevent patient, family, and staff distress or injuries. Once symptoms are under control, start reducing the dose to the minimal effective quantity [54, 55]. One of haloperidol's main side effects is extrapyramidal symptoms, which could be confused with worsening agitation [56].

If agitation persists with increasing haloperidol doses, agents providing more sedation, such as chlorpromazine or an atypical antipsychotic (e.g., olanzapine), may be considered. Studies have shown some promise using subcutaneous olanzapine to treat agitated delirium in the advanced cancer patient population [57]. Sometimes an infusion of haloperidol or more sedating neuroleptic medication (such as chlorpromazine) may be required, at which time we encourage palliative care or psychiatric consultation [27, 58, 59]. Table 43.4 lists common medications used in the management of delirium and their main side effects [57, 60, 61].

Chlorpromazine is a more sedating antipsychotic, but its use is limited by significant side effects, such as orthostatic hypotension and anticholinergic effects. Benzodiazepines are not recommended (except in alcohol withdrawal) or if antipsychotic medications are contraindicated or associated with significant side effects (seizures, extrapyramidal side effects, or severe arrhythmia). In such cases, consultation to palliative care, psychiatry, or neurology specialists is recommended [62–64].

Table 43.4 Common medications for management of agitated delirium

Medication	Main receptors affected	Available forms	Major side effects
Haloperidol	Dopamine D2, D1	Oral Subcutaneous Intramuscular Intravenous	Extrapyramidal QT-interval prolongation Seizure *Use lower doses in elderly or frail patients
Chlorpromazine	Dopamine D2, D1 α1-Adrenergic	Oral Rectal Intravenous Intramuscular	Orthostatic hypotension Anticholinergic QT-interval prolongation Arrhythmia
Risperidone	Serotonin 5-HT2A α1-,α2- Adrenergic Histamine H1	Oral	Arrhythmia Dysphagia Seizure Expensive *Use with caution in patients with severe hepatic or renal dysfunction Use lower doses in elderly or frail patients
Olanzapine	Serotonin 5HT2A Histamine H1 Muscarinic M1	Oral Subcutaneous Intramuscular	Arrhythmia Weight gain Sedation Expensive *Use with caution in patients with hepatic dysfunction
Quetiapine	Serotonin 5-HT2A Dopamine D2	Oral	Arrhythmia Orthostatic hypotension Expensive
Ziprasidone	Serotonin 5-HT2A Dopamine D2	Oral Intramuscular	Drowsiness Sedation Headache Metabolic disturbances Extrapyramidal symptoms

The atypical antipsychotics have gained attention in the management of delirium; however, most of these agents are unavailable in parenteral form. For atypical antipsychotic agents available in the parenteral form, such as olanzapine and ziprasidone, administration via intramuscular injection is recommended. Such routes may not be suitable for the advanced cancer patient, who frequently suffers from muscle wasting and cachexia or has thrombocytopenia or other hematologic abnormalities. Antipsychotic side effects depend on the receptor targeted or blocked by the medication. For example, chlorpromazine's action on histamine and α1-adrenergic receptors results in more sedation and orthostatic hypotension, respectively, than does haloperidol. Conversely, haloperidol has more extrapyramidal side effects because of its action at dopamine receptors [63, 65, 66].

Some studies have reported increased mortality in elderly patients receiving atypical antipsychotic medications, resulting from their effect on cardiac conduction. This mortality may be due to prolonged QT intervals and resultant arrhythmias. Therefore, it is vital to obtain a baseline ECG, if possible. If conduction abnormalities are evident at baseline, antipsychotics should be used sparingly.

Step 4. Treating the Underlying Cause

Opioid Toxicity Rotate (switch) opioids from one type to another based on the morphine equivalent dose of the new opioid and reduce the dose of the new drug as recommended for pain management. If the ED physician lacks experience in pain management, consider pain or palliative care consultation. Hydration may be required to clear active metabolites.

Sepsis Start intravenous fluids and appropriate antibiotics as soon as possible.

Other Drugs Discontinue all possible implicated medications, especially benzodiazepines, anticholinergics, corticosteroids, antidepressants, certain antiemetics and antivirals, antibiotics (quinolones), cimetidine, and ranitidine.

Dehydration Start intravenous or subcutaneous hydration as soon as possible. In the home or hospice settings, fluids may be given under the skin (hypodermoclysis) with normal saline at 60–100 ml/hour or give boluses of 500 cc administered over 1 hour, three or four times daily.

Hypercalcemia Treat with hydration with saline and bisphosphonates.

Hypoxia Treat the underlying cause and administer oxygen.

Table 43.5 Interventions to correct common underlying causes of delirium

Condition	Treatment
Side effect of a medication (e.g., opioids, benzodiazepines)	Stop offending drug (with opioids, consider reducing dose/switching to a different opioid)
Alcohol or benzodiazepine withdrawal	Benzodiazepines
Dehydration	Intravenous fluid hydration
Infection/sepsis	Antibiotics
Hypercalcemia	Hydration, bisphosphonate, or calcitonin (for hypercalcemia)
Brain metastasis	Corticosteroids (consider radiation therapy or chemotherapy)

Brain Tumor or Metastasis Consider high-dose corticosteroids. Radiation or surgery may be required. Table 43.5 lists possible interventions to correct the underlying cause of delirium.

Step 5. Counseling the Patient's Family and Healthcare Professionals

Confusion and agitation are expressions of brain malfunction and not necessarily of discomfort or suffering. Disinhibition is one of the main components of delirium and may result in two possibly distressing phenomena:

- *A dramatic expression of previously well-controlled physical symptoms by grimacing or moaning*: Family or staff may interpret this as aggravating symptoms rather than merely increased expression. In addition to observer distress, this can lead to excessive use of opioids and adjuvant drugs, as well as the accompanying potential for delirium exacerbation.
- *Unreasonable requests of family or staff* (e.g., "I want to go home now."): If these requests are not immediately addressed, the patient may become hostile. Unless appropriately explained to the patient's family, this disinhibited behavior may be quite distressing. Research has shown that up to 74% of patients recall their symptoms after delirium resolution and up to 81% of those recall associated distress [67]. Hypoactive delirium is as distressing for patients as hyperactive delirium.

Palliative Sedation

Palliative sedation (PS) is defined as "the monitored use of sedative medication to reduce patients' awareness of intractable and refractory symptoms near the end of life, when other interventions have failed to control them." Clinicians should attempt all available symptom-specific measures,

including specialists' consultation before labeling a symptom as refractory. Refractory delirium is the most common indication for PS [68].

The goal of PS is to control distressing symptoms and not to hasten death. Consciousness should be maintained if possible. PS should be differentiated from physician-assisted death or euthanasia. Therefore, we do not recommend PS for existential distress. Reasons and goals of PS should be discussed with the family and patient (if possible) and well documented in the medical record [68].

Midazolam is the drug of the first choice. Use the lowest dose possible to provide comfort, e.g., commence a continuous SC or IV infusion of midazolam at 1 mg/hour, titrated according to clinical response.

Prognosis

Mortality risk varies depending on the delirium subtype, as well as potential etiological factors involved. The hypoactive subtype of delirium is associated with a higher mortality rate and a shorter mean survival time [17].

Delirium is associated with increased risks of complications, more extended hospital stays, prolonged mechanical ventilation, and increased mortality rates. Delirium has also been suggested as a risk factor for the future development of dementia. Patients who do not recover fully continue to show signs of cognitive impairment and functional decline over time [69].

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Suicide

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Anis Rashid

Introduction

Suicide is the intentional act of taking one's own life. The traits dependent on heritable factors related to suicidal psychopathology are complex. The triggers leading to suicide vary from severe depression to loss of a loved one, loss of a job, hopelessness, substance misuse, chronic or incurable illness, and even uncontrollable anger due to an underlying clinical or psychiatric illness. According to the World Health Organization, about 800,000 people die by suicide worldwide every year [1]. Suicide is the second leading cause of death in individuals aged 18–24 years and the fourth leading cause of death in older populations [2].

Cancer patients have a four times higher risk of suicide as compared to the general population [3]. One study found that 8% of patients attending an oncology clinic reported ongoing passive suicidal thoughts [4]. Chochinov et al. documented that up to 44% of terminally ill cancer patients expressed fleeting suicidal thoughts [5]. Cancer patients are at high risk for suicide as they are burdened with cancer-specific risk factors in addition to the general risk factors for suicide. Major risk factors specific to cancer patients include pain, physical dysfunction/dependence, and a fear of abandonment [6]. Literature indicates that the risk of suicide is highest in the first year and the relative risk is highest in the first month after a cancer diagnosis but decreases significantly over time [6]. Increased risk may resurface with advanced stage or recurrent disease. A higher risk of suicide has been reported in patients with certain cancer types such as lung cancer, head and neck cancers, Hodgkin lymphoma, testicular cancer, and bladder cancers [3]. Studies have shown that elderly, white, unmarried men are at greater risk than other patient groups [3] and as compared to patients with spousal support [7].

Whether in the general population or in an oncology setting, the act of suicide has a traumatic effect not only on the person's family, relatives, close friends, and caregivers but also on coworkers, colleagues, organizations the person was part of, and even the entire community. Caregivers of cancer patients may be more traumatized, as in addition to grief they may feel they have failed in providing proper emotional and physical support to the patients [8]. Suicide has repercussions far beyond the affected individual. In summary, the act of suicide has negative ripple effects throughout society. Confidentiality is the key to preservation of trust between clinicians and patients, but when there is a threat of harm to self or others, clinicians have a duty to breach confidentiality and take necessary actions to protect identifiable individuals. Recognizing and reporting suicidal individuals whose job functions could endanger the safety of others is crucial.

A few years ago, one such suicide changed the dynamics of the airline industry, with global repercussions. On March 24, 2015, Germanwings Flight 9525, an Airbus 320, took off for a two-hour flight from Barcelona to Dusseldorf. An hour and half into the flight, the Airbus 320 crashed into the Alps 100 kilometers northwest from Niles killing all 150 people on board. The cause of the crash, determined by an investigation, was an act of suicide committed by the copilot, 27-year-old Andreas Lubitz. The suicide shook the airline industry worldwide. Subsequently, it was determined through an investigation that the copilot had a long history of severe depression and was on several psychotropic medications. He had seen his psychiatrist 2 weeks before the incident. German privacy laws prevented this information from being shared with his employer. This lack of information prevented any timely intervention by his employer or a third party. The result was a terrible suicide that took both his life and that of 149 innocent people. It also brought into focus the question of privacy laws in relation to conditions relevant to critical job functions.

In the United States, the patient physician relationship is confidential, and the Health Insurance Portability and Accountability Act (HIPAA) protects the confidentiality of health records, including therapy and mental health infor-

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mation, but with certain exceptions. Confidentiality can be breached if the patient is a threat to his/her own safety and safety of others [9].

Despite advances in cancer treatment and success in novel approaches of treatment with immunotherapy, the diagnosis of cancer can still feel like a death sentence to some patients. Patients can feel anxiety, depression, and compromised quality of life due to the sheer burden of undergoing cancer treatment. Regular support, reassurance, and medication management by mental health providers give them hope, improve their quality of life, and keep them adherent to medical treatment. Continuity of care and empowering them with emotion-based coping strategies are essential for their stability.

Case Study: Refractory Hodgkin Lymphoma

Mr. B, a 40-year-old gentleman with refractory Hodgkin lymphoma, was seen over several years in the psychiatry clinic for anxiety and depression. He was stable with medications and psychotherapy. However, Mr. B lost his mental health insurance and was not seen in the clinic for several months. One afternoon a social worker from the lymphoma team contacted the psychiatry clinic, explaining that Mr. B is extremely distressed, is back on mental health coverage, and needs to be seen urgently. Mr. B walked into the psychiatry clinic limping, with his head down, and spoke in a low tone. He stated he was miserable due to CAR T-cell toxicities and feels he is better off being dead. He denied any active suicidal thoughts or plans but reported he cannot live like this and intends to stop the treatment. He came to psychiatry clinic at the social worker's insistence.

Mr. B had failed several lines of chemotherapy and stem cell transplant. The disease progressed, and he was then started on immune checkpoint inhibitor. Mr. B developed severe toxicities related to the treatment which compromised his quality of life. He was fatigued and developed bilateral lower limb vasculitis with open wounds, abdominal pain, diarrhea, bilateral hip pain, neuropathy in hands and feet, and a wrist drop. He became severely depressed and started having fleeting suicidal thoughts. Mr. B reconnected with his psychiatrist and assured her that he would not harm himself because of his faith. As he had no active suicidal thoughts, no past history of suicidal attempt, and a good support system, he did not seem to be at acute risk for suicide. He was discharged home with close follow-up and was given suicide hotline numbers and the social worker's direct contact information. Social work's timely intervention and support from psychiatry services, as well as a modification in his cancer treatment regimen, has stabilized Mr. B. He is back to his baseline mood, compliant with his cancer treatment, and stable enough to enjoy company of his friends and his favorite television programs.

It has been well established that not all individuals who commit suicide truly want to die. Most suicidal patients have a desire to live; they either cannot see past their distress to the options available or have lost hope of changing their situation. It is important to be able to assess who will commit suicide and who is just thinking about it. The relationship between depression and suicide has been well documented in the literature; however, not everyone with depression wants to die or attempts suicide. This suggests that depression is not fully adequate as a causal explanation and that additional factors play a role in suicide. Although the act of suicide is complex, several theories have been described to explain the extent of deep emotional pain and reasoning that triggers the act. In this chapter, we describe these theories and the biopsychosocial model of suicide. We then discuss risk factors specific to cancer patients and management of suicidal patients in oncology settings. Finally, we propose directions for future research.

Theories of Suicide

Mental health providers have been trained to understand the psychopathology underlying suicidal thoughts. Psychoanalysts have several theories regarding suicidal ideations and gestures. According to Freud, suicide is aggression turned inward [10]. He believed that patients internalize and connect with an object (person) so deeply that they and the object become one entity. If in their minds that object betrays them, they become angry and believe that the only way to get rid of the object is to get rid of themselves [10]. Karl Menninger claimed suicide reflects murderous wishes of individuals who kill themselves [11]. Edwin Shneidman described the unbearable psychological pain and suffering that exists in the mind of a suicidal person [12]. He talked about the imbalance between belongings and the burden. He believed that individuals with major losses and failures in life may feel overpowered by psychological demands that are above their tolerance threshold. This intense psychological energy can lead to an impulsive desire to change the unbearable situation [12]. Aaron Beck's theory of suicide is about hopelessness: that nothing will change for the better no matter what an individual does [13]. Another theory of suicide by Roy Baumeister is based on persistent negative experiences in life leading to negative self-perception and self-hate, with the only escape being suicide [14].

Biopsychosocial Model of Suicide

Introduced about 45 years ago, the biopsychosocial model was developed to better understand patients by using a more holistic approach with less emphasis on biomedicine. This model,

which captures the interaction of biological, psychological, and social factors underlying illness, can help nonpsychiatric clinicians understand the underlying complex psychopathology that may manifest as physical symptoms in their patients [15]. With time, the biopsychosocial model became very popular and currently has become the standard of practice in teaching programs for medical students and residents.

Unfortunately, the concept and practice of this model have changed overtime and have now drawn an artificial distinction between biology and psychology. Psychiatrists have become psychopharmacologists, and the role of psychotherapy has been taken over by psychologists. One of the reasons for this divide is the difference in reimbursement from insurance companies for pharmacological management versus psychotherapy.

Trained in the concept that any psychopathology may have biological and social influences, mental health providers are highly interested in examining **three** domains: **predisposing, precipitating**, and **perpetuating** risk factors for suicide. Predisposing factors include patients' genetic makeup, temperament, and social factors during early childhood. Precipitating factors include stressful life events and losses affecting psychology. Perpetuating factors are ongoing life challenges [16]. The biopsychosocial formulation gives clinicians a deeper understanding of such factors as patients' unhappy childhoods, poor social support and relationships, anger, negative cognitive style, and impulsivity.

Predisposing Factors: Genetic Makeup

Serotonin

One of the complex aspects of the neurobiology of suicide is that of serotonin. Dysregulation of serotonergic receptors in the brain plays an important role in depression and suicidal behavior. Serotonin is the main neurotransmitter that plays an important role in mood [17], appetite, sleep, and memory [18]. It has been well documented that cerebrospinal fluid in depressed patients who committed suicide contained lower levels of 5-hydroxyindoleacetic acid, which is the major metabolite of serotonin, as well as lower levels of homovanillic acid, a metabolite of dopamine [19]. Lower levels of serotonin could be due to upregulation of serotonin receptors [19]. In order to compensate for lower serotonin levels, the body attempts to enhance serotoninergic activity at nerve terminals by increasing central serotonergic neurons and the levels of key enzymes required for serotonin synthesis. This complex phenomenon is still not clearly understood.

Hypothalamus-Pituitary-Adrenal Axis

A more recent study focused on the hypothalamus-pituitary-adrenal axis in depressed patients and confirmed hyperfunctioning of the axis in depression and return to normal functioning when symptoms improved. The study used the dexamethasone suppression test and found a much higher positive rate in depressed patients with suicidal behavior vs. depressed patients with no previous suicidal thoughts. This indicates suicide-specific characteristics that may differentiate depressed patients with suicidal behavior from those without such behavior [20]. Further work is needed in the area.

Childhood Trauma

Other associated factors affecting suicidal thought include adverse childhood experiences in the absence of protective factors. Children raised in a household with parental substance use or incarceration and divorce or domestic violence or those who experience childhood sexual, emotional, or physical abuse develop a sense of insecurity, mistrust, and anger [21]. It has been shown that childhood trauma alters stress reactivity of the hypothalamus-pituitary-adrenal axis [22]. As adults, these individuals may develop physical, mental, and behavioral disorders with poor coping skills and feel very angry with themselves and society. Depression may result, and when individuals have other risk factors such as substance misuse, mistrust, and poor social support, they are at high risk for suicide.

Anger and Impulsive Behavior

Another well-known risk factor for suicide is anger and impulsiveness in individuals. These characteristics can play an important role in enhancing the risk of suicide [23, 24]. Teenagers and young adults are more impulsive, which may increase the risk of suicidal behavior [25]. This may be due to poor self-control and urgency to act on thoughts, disregarding implications and consequences.

Precipitating Factors

Mood Disorders

A strong association between suicide and depression has been documented [26]. The literature suggests that almost 90% of people who commit suicide have a mental disorder but only 5% of people with a mental disorder die by suicide [27]. Thus, depression in itself does not always lead to suicide. The stress-diathesis model describes the tendency to act upon suicidal ideations as based on multiple factors and not just the presence of a mental disorder such as depression [27]. Sometimes, unpleasant life events such as loss of a loved one or a relationship with extreme hopelessness may be so devastating that they lead to suicide [28].

Substance Misuse is an independent risk factor for suicide. Compared to the general population, people with alcohol and drug use disorders have a 10–14 times higher risk of suicide [29].

Chronic Illness

Patients with chronic illnesses, such as rheumatoid arthritis, diabetes, or cancer, may grieve for the loss of the life they experienced before being sick. Adjusting to the prolonged illness and effects, such as loss of employment, financial distress, or poor quality of life, is difficult. Such individuals may have protracted distress, develop depression and suicidal thoughts, and may even attempt suicide. Patients with chronic illness who have poor social support and quality of life are at high risk for suicide [30].

Challenges Faced by Military Veterans

The majority of first suicide attempts in veterans occur after separation from military service; veterans may find it difficult to adjust to civilian life due to relationship conflict, social isolation, pain from war injuries, and symptoms of post-traumatic stress disorder [31].

A 2019 report released by the Veterans Administration stated that the suicide rate among veterans is 1.5 times higher than among nonveterans [32, 33]. The literature indicates that major factors responsible for the high suicide rate in veterans are habituation and the acquired capability to attempt suicide [34]. Through repeated exposure to trauma or near-death experiences while serving on the front lines, soldiers may become habituated to trauma, injury, and death, and the fear of death may fade away. Another risk factor in this setting is survivors' guilt [35].

Financial Crisis/Loss of Job

Economic trends and industry shifts, such as corporate mergers and sale of companies in capitalistic economies or changing market forces, can cause major upheavals in individual lives through unemployment, loss of business, and failure to be able to support oneself. Many poor countries in Africa, South America, and Southern Asia are also known to have high suicide rates due to chronic hopelessness associated with the failure to earn enough income to raise a family or take care of the sick and elderly [36]. Again, the will to survive can vanish, propelling individuals in a highly distressed society to attempt suicide as a way to escape their financial conditions.

Environmental Factors

Environmental influences are well known to play a role in suicidal thoughts. Changes in human behavior triggered by negative external events can strongly affect the body's stress system and responses. These epigenetic changes influence psychiatric disorders and may lead to suicide attempts [37].

Perpetuating Factors

According to the stress-diathesis model, an ongoing biological or psychological factor in the absence of an acute event may not influence the individual toward a suicidal attempt. However, stressful acute events, such as divorce, rejection, or loss of a loved one, can cause a strong emotional experience of hopelessness and, when combined with impulsiveness, propel an individual toward suicide.

Suicide Risk Factors Specific to Cancer Patients

Although the literature documents a high risk of suicide in cancer patients, thus far, there is no clear documentation that cancer, *in and of itself,* is a risk factor for suicide in the absence of any psychopathology [38]. The risk of suicide in this patient population is high, however, since, in addition to general risk factors discussed above, cancer patients face other risk factors, including disease burden and life-changing adverse effects of cancer treatment. In the initial stage of disease, patients are anxious and fearful, with uncertainty of treatment outcome, and may experience treatment side effects, including nausea, poor energy, and sleep disturbances. As the disease progresses or treatment intensifies, patients may experience extreme fatigue, poor appetite, vomiting/diarrhea, neuropathy, and physical changes such as loss of muscle mass, loss of hair, and discoloration of skin and nail beds. Patients may lose their jobs and their physical independence. Depression may set in as the patient becomes more dependent on others. Role reversal within the family that comes with loss of independence, job loss, financial distress, and the potential guilt of being a burden on the family can intensify symptoms of depression.

In addition to hopelessness and fear of abandonment, one of the major risk factors for suicide in cancer patients is intolerable pain and suffering. Reports have documented that cancer patients do not always experience good pain control; for example, oncologists may fear prescribing opioids to emaciated or ill cancer patients with compromised liver, kidney, or respiratory functions.

Management of Suicidal Cancer Patients

Currently, the best screening tool is the clinical judgment of mental health providers and their expert opinions regarding suicide risk. Such providers working with these patients try to understand the root cause of these symptoms and provide support and management strategies. When a patient with cancer reports suicidal thoughts, it should be given serious consideration. It is important to determine whether such thoughts are due to physical challenges, such as unbearable pain, or because of hopelessness and depression. Many symptoms of depression, such as poor sleep, fatigue, and loss of appetite, are similar to those of cancer and the side

effects of cancer treatment. Hopelessness, loss of meaning in life, despair, and suicidal thoughts are alarming signs [39]. Cancer patients with a history of psychopathology, previous suicide attempts, or a family history of mental illness are at high risk for suicide. Recognizing clinical depression in cancer patients is very important as depression is treatable; treatment may uplift patients' mood, giving them hope and motivating them to continue treatment.

Management of Suicidal Oncology Patients in the Emergency Department

About 8% of emergency department (ED) patients have suicidal thoughts, which they may not share unless asked [40]. It is important for the emergency physician to explore any suicidal thoughts from a patient with a history of mental illness. Based on the initial assessment, the clinician may need to consult the psychiatry service for a full evaluation and management. Management of suicidal oncology patients in the emergency department is a challenge due to time constraints, medical comorbidities needing immediate attention, the potential need to find availability of psychiatry beds in a med-psych facility, arranging transport to the appropriate hospital, and completing paperwork for involuntary admission, if the patient is not willing to go voluntarily.

The first step in management is to implement a proper safety protocol and protect the patient from self-harm. Patients with suicidal thoughts should not be allowed to leave the emergency department until they have had a complete evaluation by a mental health provider [41]. Medical staff should closely observe the patient, and the room should be searched for items that could be used as a weapon, such as a belt, wires, any sharp object, or glass medicine bottles [41].

Patients with vague suicidal thoughts but no plans, no previous attempts, no history of mental illness, no substance use, no agitation or confusion, and with good social support may be allowed to leave but with a firm follow-up plan [42], as the days after discharge from the emergency center are a high-risk period [40]. Patients who have any unbearable physical symptoms such as pain or severe nausea and vomiting should be admitted to the medical ward for stabilization and control of these symptoms.

Cancer patients with active suicidal thoughts who are undergoing active treatment or with medical comorbidities should be admitted to a hospital where they can be monitored closely until stabilized and their treatment continued. Daily assessment by a mental health provider, appropriate medication, and support are required. After discharge from the hospital, the patient should follow up with a psychiatrist for continued care.

It is important to determine if the suicidal thoughts are due to unbearable physical symptoms, such as severe pain or intractable nausea/vomiting, which should be addressed and managed properly. Inadequate pain management in oncology is a multidimensional problem. It is a devastating symptom that many cancer patients suffer. Since the publication of the analgesic ladder in 1986, pain management has improved, but many cancer patients still do not receive proper pain control [43]. High pain levels, especially in advanced cancer stages, lead to suicidal thoughts. Pain symptoms should be properly managed by the palliative care team [7] during hospitalization, and patients should be discharged with adequate analgesics. Any other physical symptom should be properly investigated and managed.

Management of Suicidal Patients in the Oncology Clinic

Patients with active suicidal thoughts or plans to act on them require full evaluation by a mental health provider and should be admitted to a psychiatric facility for safety until stabilized. Patients with passive suicidal thoughts, with no plans and means to act on them, and with no major risk factors but good social support may be allowed to go home after thorough evaluation. With the patient's permission, a family member or a close friend can be involved who will monitor the patient's safety and adherence to treatment [42]. Such patients should be monitored through regular follow-up with a mental health provider and medication management as indicated.

Most suicidal patients do not want to end their lives; rather, they want to end their emotional pain and unbearable suffering. Talking about suicide does not trigger a suicidal attempt. Instead, it gives the patient a chance to discuss his/her fears and may help them find a source for sharing their feelings. Clinicians work in a collaborative model, walking with the patient on difficult roads to understand their emotional pain and suffering, validating their emotional turmoil, and helping them find alternative ways to cope. They assure these patients that the solution to their problems lies within them and they can work together to find those solutions [44]. They help raise patients' pain threshold and coping skills. Regular follow-up with a mental health provider for support and to learn and sustain coping strategies is key. The mental health provider develops a suicide-specific treatment plan and clinically tracks and documents ongoing suicidal risk. They also monitor medication compliance, side effects, and response. Most important is to empathize with the suicidal wish, identify protective factors, and work in a collaborative model.

The literature documents that combination therapy with medication and psychotherapy gives better results in managing depression [45]. This approach shortens the time until symptom control and increases adherence to medical treatment. Cognitive behavioral therapy and dialectal behavioral

therapy have shown good results to reduce suicidal thinking, as they address cognitive and behavioral aspects of suicide.

Antidepressants for the Treatment of Depression in Cancer Patients

Depression is the most common psychological symptom in cancer patients. It is often underdiagnosed or misdiagnosed because its symptoms overlap the physical symptoms of cancer and its treatment. The most frequent and common example of this misdiagnosis is hypoactive delirium. Prescribing an antidepressant or a stimulant to a delirious patient may exacerbate the condition [46]; hence, proper diagnosis and management of depression by a mental health provider is important. There are not enough data available to assess the efficacy and tolerability of antidepressants in the oncology setting, and no one antidepressant has been proven superior to another [47]. The most commonly prescribed antidepressants in the oncology setting are specific serotonin reuptake inhibitors (SSRIs). These drugs have a good safety profile with a minimum of drug interactions. The choice of antidepressant should be individualized to the specific symptoms in cancer patients. Patients with depression and poor sleep may be given antidepressants with sedative properties [48]. Depressed patients with pain symptoms may benefit from the choice of duloxetine. Cancer patients with nausea and poor appetite may benefit from mirtazapine; this drug not only helps with mood symptoms but also controls nausea and promotes appetite. It is important to understand that antidepressants take a few weeks to control symptoms. Psychostimulants deserve special consideration in terminally ill patients when a quick response is needed, as they provide a rapid effect [49]. Choosing an antidepressant becomes challenging when patients are on certain protocols with restrictions on the choice of antidepressant or when they are unable to swallow a pill. Communicating with the primary oncology team before starting an antidepressant, monitoring the side effects profile of the drug, and having a sound knowledge of drug-drug interactions is important.

Future Research

Patients with biopsychosocial risk factors and suicidal thoughts and behaviors may show a specific neural circuitry picture. Previous work on brain scans has identified specific circuits associated with executive functions, impulsivity, and mood [50]. Recently, it has been shown that every idea or thought has a specific pattern in the brain; these patterns can be identified through brain scans showing color changes in the brain neurons. Researchers have been working to identify suicidal thoughts through brain scans with the goal of determining who could attempt suicide in the future. People with active suicidal thoughts exhibit increased brain activity in the areas associated with emotions and thoughts about self, which can be identified using functional MRI [51]. This work is still in the initial stages but seems promising. If thought processes reflecting risk factors of suicide can be identified and associated with interventions, a reduction in suicide attempts could result.

Conclusion

Suicide remains among the leading causes of death in the United States. The management of suicidal patients is a psychiatric emergency and the most challenging task faced by mental health providers. Through an empathic and collaborative approach, clinicians in the emergency department and mental health providers can prevent future injury and death. Emergency physicians, social workers, and mental health providers should work as a team to ensure the safety of suicidal patients, reduce emotional pain, address any acute medical condition leading to suicidal thoughts, and make appropriate treatment plans. Ensuring that treatment and safety plans are followed during transitions of care, when patients are transferred to another facility or referred for follow-up appointments, is essential to providing superior care and sustained stabilization.

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Substance Abuse

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Introduction

Until very recently, discussing the problem of substance abuse in people with cancer might have been seen as having only minor clinical relevance. Certainly, the relief of anxiety, pain, and other distressing symptoms has been identified as a top priority for oncologic clinicians, and the use of medications, even those with abuse potential, has been deemed essential. Much of the literature on this subject suggests that problems of substance abuse are only infrequently encountered in oncologic. Perhaps this underestimation of the problem stems from the fact that much of this academic work has come from tertiary care settings—where those with histories of addiction are less frequently encountered because of barriers to care in the form of economic issues, lack of insurance coverage, and estrangement from healthcare providers who might diagnose and refer patients to such centers. Or perhaps it has been that cancer typically remains a disease of the sixth decade of life and beyond, whereas addiction overwhelmingly manifests earlier in life, making it unlikely to emerge de novo in a person first exposed to substances with abuse potential when they are older and ill [1, 2]. Or perhaps it has been because cancer used to follow an almost uniformly fast and fatal trajectory, and so any exposure to controlled substances was likely to be brief and occur during a period of time when the person was becoming increasingly disabled and less likely to engage in practices related to the obtaining and use of illicit drugs. Thus, even if the exposure to such drugs might trigger a relapse in a person who suffered with the disease of addiction before they became ill with cancer, the dysfunctional behaviors that might have been set in motion would be mediated and limited by the relentless impact of the cancer itself. Or perhaps it was simply the trivialization of addiction that characterized the early rhetoric accompanying the increase in opioid prescribing that led to this being such a neglected topic [3].

In response to the public health crisis that is chronic pain in our aging society, the prescribing of opioids and other controlled substances increased dramatically. Unfortunately, a parallel set of public health crises arose: the problems of prescription drug abuse, diversion, overdose, and death. Although a substantial portion of the problem of opioid-related overdoses now appears to be fueled by the prevalence of illicitly manufactured fentanyl, prescription opioids remain a central concern [4]. Given that people with cancer are living longer at all stages of disease, including those with painful but stable disease and those who go onto remission but are left with chronic pain issues from chemotherapy and other factors, exposures to controlled substances are considerably longer than they once were, and thus there is greater opportunity for those who come to the disease with a history of substance use disorder (SUD) to lose control and overuse or even have the problem of addiction fully rekindled [5, 6]. Thus, it is not surprising that there has been a substantial increase in the number of opioid-related emergency department (ED) visits from patients with cancer [7], with nearly a fifth of cancer patients in the ED admitting to past or current misuse and a third at high risk of misusing their opioid prescriptions [8].

The recently exacerbated problems of opioid abuse and overdose also affect patients who do not themselves suffer from these problems. A growing concern for those prescribing controlled substances and treating pain, anxiety, and other symptoms in people with cancer, including older patients, is that their medications are increasingly sought after by younger individuals with substance abuse problems

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in their family or social environment (including grandchildren and caregivers). Additionally, recent data suggests that some parents of children with cancer do not manage their children's opioids safely, at times giving them to another person or even taking the opioid themselves [9]. Thus, it is not surprising that in the midst of the current opioid crisis, new restrictions and limits have emerged on the prescribing of opioids, including in the ED [10]. Although the intended aim of these restrictions is to address the management of acute, non-cancer pain, cancer patients in the ED and elsewhere may be impacted. An unintended consequence of the recent well-intended restrictions has been to increase the stigmatization of patients in pain, with deleterious effects on healthcare outcomes [11, 12]. Cancer patients are not immune to this burden, as evident in the lack of adequate pain control experienced by some opioid-tolerant cancer patients in the ED [13]. Mitigating the impact of stigma on pain and opioids requires a better understanding of addiction.

Thus, it is not only important for oncologic professionals of every stripe to have a working knowledge of addiction medicine principles and practices but particularly the oncologic ED professional. In the ED, consequences of drug abuse—from the older person with cancer presenting in withdrawal because family members have stolen their medication to the younger person whose addiction has been rekindled by the need for pain medication—are likely to be common. Common doesn't mean obvious, however, and it is important to dispel myths about the relative absence of addiction issues in cancer to help emergency care providers anticipate such problems and learn to manage them.

The increasing use of opioids in non-cancer pain grew out of recognition that people with cancer pain (at least those seeking treatment at tertiary care facilities) appeared to be able to take these medications with generally positive results. That is, their pain was controlled, side effects manageable, functional status improved or stabilized, and problems of misuse or addiction minimal. Opioid prescribing then increased dramatically, particularly in North America, to the much more diverse population of those with chronic pain—more diverse in terms of age, psychiatric, and addiction histories and comorbidities, as well as in duration of exposure [14]. Not surprisingly, the results of this effort were mixed. Cancer pain management with opioids follows a basically self-titration model consistent with an assumption that risk of misuse and addiction is uniformly minimal across patients. When this method of delivering opioid therapy in non-cancer pain began to meet with problems of abuse and diversion, a risk stratification model began to emerge. Younger age, personal or family history of addiction, history of sexual trauma, and active psychiatric comorbidity were seen as risks for a poor outcome in opioid therapy, unless the delivery of this therapy was tailored to the needs of the individual (with the employment of safeguards such as urine drug testing, prescription monitoring programs, and the like, as well as consultations with psychiatric and addiction professionals to assure safety). There is a certain irony in the fact that oncologic pain management must now take a page from the non-cancer pain "playbook." This type of risk stratification is somewhat foreign to oncologic pain management, but it seems that the time is right to close the loop and for the therapy that initially influenced non-cancer pain practice to adopt strategies developed therein, especially now that many of the differences between cancer and non-cancer pain patients have narrowed [15].

Pain and anxiety management are not the only aspects of cancer care affected by the presence of a SUD. Indeed, because unchecked drug or alcohol abuse can cause spotty or complete nonadherence to potentially lifesaving cancer treatments, virtually every step along the disease trajectory, from diagnosis to palliative care, can be threatened. Thus, the "downstream" complications of substance abuse can lead to a person with cancer presenting in the ED with problems related to nonadherence of every variety. A question is whether the ED professional will recognize them as such. And if the ED professional is working outside of a tertiary care academic center, the frequency with which they will be confronted with SUDs is shockingly high, due to the high base rate of these disorders in this population which is so much more reflective of the population as a whole. Particularly when one considers that substance use can be a risk factor for cancer, one would expect substance abusers to be over- and not underrepresented in the oncologic population. Many oncologic ED professionals from nearly all of the disciplines represented in this group of practitioners are lacking in their knowledge of addictions. There is an enormous gap between the prevalence of these problems and the expertise available to care for cancer patients who are struggling with them. It is hoped that this chapter helps bridge this gap for oncologic emergency medicine.

Scope of the Problem

Substance Use Disorder

Substance use disorders are a consistent phenomenon in the USA over time, with estimated base rates of 6–15% [16–20]. This prevalence of drug abuse certainly touches medically ill patients and can negatively influence how patients are treated. Although few studies have been conducted to evaluate the epidemiology of substance abuse in patients with advanced illness, these disorders have been reported to be relatively rare within the tertiary care population with cancer and other advanced diseases [21–23]. However, the prevalence of alcoholism in major cancer centers is most likely underestimated. A study by Bruera and colleagues [24] of

100 terminally ill alcoholic cancer patients found that despite multiple hospital admissions and screenings, only one-third had documentation of alcoholism in their medical records. How then would the ED professional know to anticipate and plan for emergent problems related to alcohol abuse in a person presenting in their setting?

The belief that drug habits diminish and vanish with age is no longer held with the certainty of past belief. An early study supporting this belief reported that 50% of individuals addicted to narcotics were no longer active drug users by age 32 and over 99% were no longer users by age 67 [25]. However, as the "baby boom" cohort ages, the extent of alcohol and medication misuse is predicted to increase significantly because of the combined effect of the growing population of older adults and cohort-related differences in lifestyles and attitudes [26]. One study suggested that the number of illicit drug users aged 50 years or older will double from the year 2000 to the year 2020 because of an anticipated 52% increase in this segment of the population and the attendant shift in attitudes and historical experiences with substance use in this cohort [27].

Prescription Drug Abuse

The use of illicit drugs and the nonmedical use of prescription opioids have increased significantly in the general population over the last decade, though it has begun to decline in the just the past few years, and the highest prevalence remains among younger adult men [16, 28]. Such estimates, however, belie alarming trends emerging among older adults. Among adults aged 50 or older, nearly five million, roughly 5% of that age group, report using illicit drugs in the past year [20]. Marijuana is the most abused drug in the USA, but among adults aged 60 or older, the abuse of prescription drugs is equally common. A changing pattern of cannabis use among older adults suggests that as an individual ages, the social incentive to smoke marijuana decreases, while the attempt to use it medicinally increases [29]. In the oncologic setting, this might include an attempt to self-medicate for nausea, anorexia, pain, and anxiety or combinations of these common symptoms [30]. More alarming than rates of cannabis use, ED visits related to pharmaceutical abuse more than doubled from 2004 to 2008 among adults aged 50 or older, and a fifth of these was among adults aged 70 or older [31]. Prescription opioids were the most common culprit, followed by benzodiazepines. Although ED visits in 2008 related to illicit drug use among adults 50 and older were a little less than half that of pharmaceuticals (118,495 vs. 256,097 visits), they were not uncommon [31, 32]. The majority of those visits were related to cocaine, followed by heroin. Consistent with this, one study demonstrated marijuana, cocaine, and opioid use in 2.4%, 1.9%, and 11.6% of elderly men, respectively [33]. Substance use treatment admissions among adults aged 50 and older have nearly doubled in recent years, from 6.6% of all admissions in 1992 to 12.7% in 2009 [34]. During this same time period, alcohol as the only substance of abuse being treated decreased from 87.6% to 58.0%, while the addition of other drugs to alcohol increased from 12.4% to 42.0%. Also around this time, treatment admissions involving heroin more than doubled, from 7.2% to 16.0%, and those reporting multiple drugs of abuse nearly tripled [35].

Even as the baby boomer population ages and more frequently experiences pain, there is a paucity of information on older patients and the risk of comorbid pain and SUDs. A survey in Denmark revealed that 22.5% of men and 27.8% of women aged 65 and older reported chronic pain [36]. Of these men and women, 35% of them were not satisfied with their pain treatment. This can lead to alternative methods for relieving pain such as taking non-prescribed medications. In one study of 100 patients with chronic pain (average age near 50), 23 tested positive for illicit drugs, and 12 tested positive for opioids, even though they had no prescription and denied taking opioids [37]. In another study of primary care patients in a Veterans Affairs facility who were receiving opioids for the treatment of chronic pain (average age 59), 78% reported at least one indicator of medication misuse during the prior year, with significantly more of those who misused pain medications reporting comorbid SUD [38]. This is consistent with a more recent examination of a subset of data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system's finding that though severe chronic pain is common in adults entering treatment for prescription opioid abuse, it is exponentially more prevalent in adults older than 45 years (70%) relative to the 18–24-year age group (45%) [1]. Clearly, to the extent that chronic pain and SUDs are comorbid or mutually exacerbating problems, older adults are a particularly vulnerable population. This might be especially true in the oncologic culture, wherein performing a risk assessment has been historically uncommon and decreasing patients' wariness about using opioids aggressively when needed has been the biggest concern.

Thus, the emerging pattern, consistent with the aging of the "baby boom" generation and their greater likelihood of exposure to various types of drugs, is that illicit and prescription drug misuse and abuse, along with the need for treatment, is expected to double by 2020 (relative to the 1990s prevalence estimates) among older adults [27, 39], with the greatest changes reflecting the increasing rates of ED visits and treatment admissions related to prescription opioids, benzodiazepines, heroin, and cocaine. Knowledge of these trends should assist oncologic providers in identifying and managing problems in a more age-appropriate manner.

Alcohol

There have been relatively few studies examining the prevalence of alcoholism in an oncologic population. The prevalence likely varies widely from one cancer to another with the highest rate in the head and neck cancer population. One study found that greater than 25% of patients admitted to a palliative care unit had problems with alcohol abuse [24]. Socioeconomic barriers such as low income or unemployment, lack of health insurance, and possibly even attempts to self-medicate early symptoms of cancer may preclude patients from seeking care at tertiary care centers. Furthermore, alcohol abuse complicates cancer care. For example, postsurgical withdrawal and delirium tremens (DTs) can be life-threatening. Unfortunately, many patients are unrecognized prior to undergoing surgery. Integrating screening for alcoholism and offering detoxification ahead of surgery are underutilized opportunities, discussed in detail later in this chapter.

Diagnostic and Treatment Issues

Defining Substance Use Disorder and Addiction in the Medically Ill

It is difficult to define substance use disorder (SUD) and addiction in patients with cancer, as the definitions of terms have been adopted from populations that do not necessarily have a medical illness. Furthermore, the pharmacological phenomena of tolerance and withdrawal may be present in SUD but are distinct from it, and it is important that clinicians understand the difference. To complicate the matter further, the use of these terms is inconsistent across settings and is so influenced by sociocultural considerations that it may lead to confusion in the clinical setting. In some settings, the terms "abuse" and "addiction" have been shunned in favor of the less stigmatizing "substance use disorder." (In this chapter, we use these terms somewhat interchangeably.) What these concepts have in common is some degree of the use of illicit drugs or the non-medical use of prescription medications, and at the most severe end of the spectrum there is craving and continued or compulsive use despite harms. Harms may be social, physical, psychological, or vocational in nature. The severity of the SUD depends, in part, on the harms and whether those harms are actual or potential. For example, a patient who continues to smoke following a lung cancer diagnosis likely has a more severe addiction than a smoker without cancer, even though they may smoke the same daily amount. This distinction is clinically relevant because understanding the severity helps determine the needed level of medical response. A thorough review of this topic is beyond the scope of this chapter, but we hope that some clarification of the terminology will help improve the diagnosis and management of substance abuse when treating patients with advanced disease [40, 41].

Physical Dependence: An expected biological adaptation to a drug that results in tolerance and withdrawal. Physical dependence is distinct from SUD or addiction which may involve craving and continued or compulsive use despite harms.

- "Tolerance" occurs when a higher dosage of a drug is required over time to achieve the same effect.
- "Withdrawal" occurs when rapid discontinuation of a medication leads to a sequalae of adverse symptoms.

Because substance use is increasingly widespread in the population at large, patients with cancer who have used illicit drugs are more frequently encountered in medical settings. Illicit drug use, actual or suspected misuse of prescribed medication, or actual SUDs create the most serious difficulties in the clinical setting, complicating the treatment of pain. However, the management of SUD is fundamental to medical therapy adherence and safety during treatment. Also, adverse interactions between illicit drugs and medications prescribed as part of the patient's treatment can be dangerous. The presence of a SUD may alienate or weaken an already tenuous social support network that is crucial for alleviating the chronic stressors associated with advanced disease and its treatment. Therefore, a history of substance use can impede treatment and pain management and increase the risk of hastening morbidity and mortality among those with advanced cancer, which can only be alleviated by a therapeutic approach that addresses drug-taking behavior while expediting the treatment of the malignancy and distressing symptoms, as well as addiction [21, 22].

Important factors when assessing drug-taking behavior in cancer patients:

- Undertreatment of associated issues, particularly pain disorders.
- Sociocultural differences in defining "aberrant" drug taking.

Varied and repeated observations over a period of time may be necessary to categorize questionable behaviors properly (Table 45.1). Perceptive psychiatric assessment is crucial and may require evaluation by consultants who can elucidate the complex interactions among personality factors and psychiatric illness.

Patients with borderline personality disorders, for example, may impulsively use prescription medications that regulate inner tension or improve chronic emptiness or boredom

Table 45.1 Differential diagnoses to consider when interpreting aberrant drug-taking behaviors

Possible alternate diagnoses for aberrant drug-taking behaviors
Anxiety
Depression
Insomnia
Problems of adjustment (such as boredom caused by decreased ability to engage in usual activities)
Borderline personality disorder

Table 45.2 Examples of aberrant drug-taking behaviors and severity

Examples of clearly aberrant behaviors	Examples of potentially aberrant behaviors
Illicit drug use	Requests for early medication refills
Intravenous injection of oral formulations	Requesting specific medications
Recurrent prescription "losses"	Patient taking extra doses of medication

and express anger at physicians, friends, or family. Psychiatric assessment is vitally important for both the population without a prior history of substance abuse and the population of known substance abusers who have a high incidence of psychiatric comorbidity [51].

Pseudoaddiction

Various studies have provided compelling evidence that pain is poorly treated in many oncologic patients [42–44]. Clinical experience indicates that the inadequate management of symptoms and related pain may be the motivation for aberrant drug-taking behaviors.

Pseudoaddiction: distress and aberrant drug-seeking behaviors that produce a similar pattern as individuals with substance use disorders; however, these behaviors actually stem from the patient seeking relief from untreated pain [45]:

- Patients are often attempting to "self-medicate," and behaviors can be considered pseudoaddictive if sufficient pain relief eliminates these behaviors.
- Physical dependence can often lead to pseudoaddictive behaviors, as clinicians do not compensate for growing tolerance to medications and therefore underdose patients.

More recent scientific advances have also provided new insight into behaviors that may be considered pseudoaddiction. Pharmacogenetic variances in the enzymes that metabolize pain medications help to explain individual differences in medication response and side effects experienced. If a patient is an ultrarapid metabolizer, they may complain that the medication is effective for a shorter period of time than is common for that medication. If a patient is a poor metabolizer, they may complain that the medication is not working or possibly continue to ask for increased amount of medication. Pharmacogenetic variations should be considered and pharmacogenetic testing implemented when a patient has an unusual response to a medication, more than expected side effect profile, and/or inefficacy at usual dosages [46].

The potential for pseudoaddiction creates a challenge for the assessment of a patient with both a substance use disorder and an advanced illness. Clinical evidence indicates that aberrant behaviors impelled by unrelieved pain can become so dramatic in this population that some patients appear to return to illicit drug use as a means of self-medication. Others use more covert patterns of behavior, which may also cause concerns regarding the possibility of true addiction.

Aberrant behaviors set in motion by poorly relieved pain can, in vulnerable patients, lead to actual loss of control of their opioids and/or other controlled substances, and so pseudoaddiction and abuse or addiction should not be considered mutually exclusive. Pseudoaddiction might be best thought of as akin to the problem of secondary alcoholism in response, for example, to an untreated panic disorder. If self-medication of panic disorder is persistent for some duration, before long a patient will likely have both problems—panic disorder and alcoholism. People taking liberties with their opioid dosing should be considered for a parallel diagnosis of addiction if attempts to improve analgesia do not lead to a relatively rapid cessation of the problematic behaviors [45]. Although it may not be obvious that drug-related behaviors are aberrant, the meaning of these behaviors may be difficult to discern in the context of unrelieved symptoms [21–23]. This can be a particularly vexing issue when the person with cancer presents in the ED. Is the presentation related to poor pain control or substance abuse, or both?

Aberrant Drug-Taking Behaviors

When a drug is prescribed for a medically diagnosed purpose, less assuredness exists as to the behaviors that could be deemed aberrant, thereby increasing the potential for a diagnosis of drug abuse or addiction. The ability to categorize these questionable behaviors as apart from social or cultural norms is also based on the assumption that certain parameters of normative behavior exist. Although it is useful to consider the degree of aberrancy of a given behavior, it is important to recognize that these behaviors exist along a continuum, with certain behaviors being less aberrant (such as aggressively requesting medication) and other behaviors more aberrant (such as injection of oral formulations) (Table 45.2). If a large portion of patients were found to

engage in a certain behavior, it may be normative, and judgments regarding aberrancy should be influenced accordingly [21–23].

We know more scientifically about aberrant behaviors, their prevalence, and meaning today than we did in the mid-1990s. We know that many patients will have at least a few aberrant behaviors in a 6-month period [47]. We also know that once a patient has demonstrated four behaviors in their lifetime, they have an 85% likelihood of meeting diagnostic criteria for substance use disorder [48]. But there is still much to be learned, confirmed, replicated, and studied.

Disease-Related Variables

Changes caused by progressive diseases, such as cancer, also challenge the principal concepts used to define addiction. Alterations in physical and psychosocial functioning caused by advanced illness and its treatment may be difficult to distinguish from the morbidity associated with drug abuse. In particular, alterations in functioning may complicate the ability to evaluate a concept that is vital to the diagnosis of addiction: "use despite harm." For example, discerning the questionable behaviors can be difficult in a patient who develops social withdrawal or cognitive changes after brain irradiation for metastases. Even if diminished cognition is clearly related to pain medication used in treatment, this effect might only reflect a narrow therapeutic window rather than the patient's use of analgesic to acquire these psychic effects [40, 41, 48]. To accurately assess drug-related behaviors in patients with advanced disease, explicit information is usually required regarding the role of the drug in the patient's life. Therefore, the presence of mild mental clouding or the time spent out of bed may have less meaning than other outcomes, such as noncompliance with primary therapy related to drug use or behaviors that threaten relationships with physicians, other healthcare professionals, and family members [40, 41, 49].

Risks in Patients with Current or Remote Histories of Drug Abuse

There is a lack of information regarding the risk of abuse or addiction during or subsequent to the therapeutic administration of potentially abusable drugs to medically ill patients with a current or remote history of abuse or addiction [40, 41]. The possibility of successful long-term opioid therapy in patients with cancer or chronic nonmalignant pain has been indicated by anecdotal reports, particularly if the abuse or addiction is remote [52–54].

Because it is commonly accepted that the likelihood of aberrant drug-related behavior occurring during treatment for medical illness will be greater for those with a remote or current history of substance abuse, it is reasonable to consider the possibility of abuse behaviors occurring when using different therapies. For example, although no clinical evidence exists to support the notion that the use of short-acting drugs or the parenteral route is more likely to cause questionable drug-related behaviors than other therapeutic strategies, it may be prudent to avoid such therapies in patients with histories of drug abuse [40, 41].

Clinical Management of Substance use Disorders in Oncologic

The greatest challenges in caring for patients with SUDs and cancer typically arise when these patients are actively abusing alcohol or other drugs. This is in part because they experience more difficulty in managing pain [55]. Patients may become caught in a cycle where pain functions as a barrier to seeking treatment for addiction possibly complicating treatment for chronic pain [56]. Also, because pain is undertreated, the risk of bingeing with prescription medications and/or other substances increases for drug-abusing patients [55]. The implementation of a more comprehensive treatment plan for such patients may indeed only be initiated after ED visit(s) bring the need for such a labor-intensive program to light.

General Recommendations

The following guidelines can be beneficial, whether the patient is actively abusing drugs or has a history of substance abuse. The principles outlined assist clinicians in establishing structure, control, and monitoring of addiction-related behaviors, which may be helpful and necessary at times in all pain treatment [21].

Recommendations for the long-term administration of potentially abusable drugs, such as opioids, to patients with a history of substance abuse are based exclusively on clinical experience. Research is needed to ascertain the most effective strategies and to empirically identify patient subgroups which may be most responsive to different approaches. The following guidelines broadly reflect the types of interventions that might be considered in this clinical context [37, 49, 57].

Multidisciplinary Approach

Pain and symptom management is often complicated by various medical, psychosocial, and administrative issues in the population of advanced patients with a substance use disorder. The most effective team may include a physician with expertise in pain/palliative care, nurses, social workers, and, when possible, a mental healthcare provider with expertise in the area of addiction medicine [21, 22].

Assessment of Substance Use History

In an effort to not offend, threaten, or anger patients, clinicians frequently avoid asking patients about drug abuse. There is also often the expectation that patients will not answer truthfully. However, obtaining a detailed history of duration, frequency, and desired effect of drug use is vital. Adopting a nonjudgmental position and communicating in an empathetic and truthful manner is the best strategy when taking patients' substance abuse histories [21–23]. Avoid stigmatizing terms such as "abuse." Do not rush through a substance use assessment: It helps to make eye contact and show the patient that you really care about their answers. Patients can be quite candid about their drug and alcohol use, though even then it is not unusual for them to underreport or minimize their problems.

In anticipating defensiveness on part of the patient, it can be helpful for clinicians to mention that patients often misrepresent their drug use for logical reasons, such as stigmatization, mistrust of the interviewer, or concerns regarding fears of undertreatment. It is also wise for clinicians to explain that in an effort to keep the patient as comfortable as possible, by preventing withdrawal states and prescribing sufficient medication for pain and symptom control, an accurate account of drug use is necessary [21–23].

Taking an accurate, detailed history from the patient is essential for the proper assessment and treatment of alcohol and drug abuse as well as any comorbid psychiatric disorders. It is also important to ask about the duration, frequency, and desired effect of drug or alcohol consumption. In the wake of current pressures to treat the majority of patients in ambulatory settings and to admit patients on the morning of major surgery, the quick identification of alcoholism and initiation of plans for social, medical, and physiological needs of the patient must begin upon initial contact.

The use of a careful, graduated-style interview can be beneficial in slowly introducing the assessment of drug abuse. This approach begins with broad and general inquiries regarding the role of drugs in the patient's life, such as caffeine and nicotine, and gradually proceeds to more specific questions regarding illicit drugs. This interview style can also assist in discerning any coexisting psychiatric disorders, which can significantly contribute to aberrant drug-taking behavior. Once identified, treatment of comorbid psychiatric disorders can greatly enhance management strategies and decrease the risk of relapse [21–23].

Use of Risk Assessment Tools

As stated above, potential opioid use must be accompanied by risk stratification and management. Given time constraints, a full psychiatric interview may not be feasible, and thus time-sensitive measures are clearly needed to help in this endeavor. Many screening tools contain items on personal and family history of addiction as well as other history-related risk factors, such as preadolescent sexual abuse, age, and psychological disease. These are tools for clinical decision-making and should not be viewed as necessarily diagnostically accurate [58, 59]. Whatever tool the clinician chooses, it is advised that the screening process be presented to the patient with the assurance that no answers will negatively influence effective treatment. One risk factor unique to the oncologic setting is the economic pressure that accompanies the disease and its treatment. The depletion of savings over time can be a huge stress, and for some the temptation to divert medications with a street value may be seen as a matter of survival.

Setting Realistic Goals for Therapy

The rate of recurrence for drug abuse and addiction is high in general. The stress associated with cancer and the easy availability of centrally acting drugs increase this risk. Therefore, total prevention of relapse may be impossible in this type of setting. Gaining an understanding that compliance and abstinence are not realistic goals may decrease conflicts with staff members in terms of management goals. Instead, the goals might be perceived as the creation of a structure for therapy that includes ample social/emotional support and limit setting to control the harm done by relapse [21–23].

There may be some subgroups of patients who are unable to comply with the requirements of therapy because of severe substance use disorders and comorbid psychiatric diagnoses. In these instances, clinicians must modify limits on various occasions and endeavor to develop a greater variety and intensity of supports. This may necessitate frequent team meetings and consultations with other clinicians; however, pertinent expectations must be clarified, and therapy that is not successful should be modified [21–23].

Evaluation and Treatment of Comorbid Psychiatric Disorders

Extremely high comorbidities of personality disorders, depression, and anxiety disorders exist in alcoholics and other patients with substance abuse histories [51]. Individuals with a history of alcohol abuse have been found to be at higher risk for other psychiatric disorders [60]. The most common comorbid mental disorders associated with alcoholism are anxiety disorders (19.4%), antisocial personality disorder (14.3%), affective disorder (13.4%), and schizophrenia (3.8%) [61]. The occurrence of comorbid mental disorders in alcoholics may contribute to poor treatment compliance and success due to cognitive limitations and premorbid (in relation to the diagnosis of cancer) pain and neurological deficits. The same is true of opioid abuse where 85% of addicts have a comorbid, nondrug abuse-related psychological disorder [51]. Thus, the ED professional assessing the cancer patient with addiction or alcoholism must anticipate and identify for treatment or referral any comorbid disorders present. The treatment of depression and anxiety can increase patient comfort and decrease the risk of relapse or aberrant drug taking [21–23].

Preventing and Minimizing Withdrawal Symptoms

Assessing and treating withdrawal can help mitigate the immediate harms, as well as preventing substance use relapse. Identifying withdrawal, as with uncovering substance misuse, is an opportunity to initiate a useful discussion with the patient. Because patients with drug abuse histories often use multiple drugs, it is necessary to conduct a complete drug-use history to prepare for the possibility of withdrawal. A thorough discussion of this topic is beyond the scope of this chapter, but we will briefly discuss opioid and alcohol withdrawal, as they can be particularly consequential and likely to be encountered in the ED. Opioid withdrawal can be extremely unpleasant but rarely results in death. However, for a patient on long-term opioid therapy for pain, withdrawal can precipitate a severe exacerbation of pain, and in an individual with an opioid use disorder (OUD), withdrawal also increases the risk of a relapse, which can sometimes be fatal [62]. Perhaps more commonly, withdrawal (and indeed sometimes the ED visit itself) can indicate that the patient may have increased their use of prescription opioids, running out early. In this case, an important question is whether there has been an exacerbation of pain secondary to a change in the disease progression. Accurately assessing withdrawal can be challenging, as the symptoms associated with different types of withdrawal can overlap. To aid in assessing withdrawal, it is helpful to utilize the substance use history, conducted in a nonjudgmental manner so as not to evoke shame and silence. Simply noticing some possible symptoms of withdrawal and inquiring with the patient can sometimes open up useful discussions. When a patient is unwilling or unable to provide this information, the clinician may rely more on the presenting symptoms, information obtained from family or friends, results of toxicology reports, and review of prescription drug monitoring programs. Some symptoms of opioid withdrawal include pain, anxiety/restlessness, insomnia, excessive sweating, dilated pupils, diarrhea/abdominal pain, flu-like symptoms, goose bumps, tremor, and yawning [63].

Alcohol Withdrawal Syndrome

Alcohol withdrawal is dangerous and can seriously complicate cancer treatment. In some instances, it is fatal. The first symptoms of withdrawal typically appear in the first few hours following the cessation of alcohol consumption and may consist of tremors, agitation, and insomnia. In cases of mild to moderate withdrawal, these symptoms tend to dissipate within 1–2 days without recurrence. However, in cases of severe withdrawal, autonomic hyperactivity, hallucinations, and disorientation may follow. The onset of delirium tremens marks the individual's progression from the withdrawal state to a state of delirium that represents a serious medical emergency.

Delirium tremens (*DTs*): characterized by agitation, hallucination, delusions, incoherence, and disorientation, typically within the first 72–96 h of withdrawal

- Occurs in approximately 5–15% of patients with alcohol withdrawal [64].
- Is self-limiting and often ends with the patient entering a deep sleep with amnesia for most of the episode.
- DTs can increase the risk of further complications in medically ill patients.

Wernicke-Korsakoff syndrome: indicative of thiamine deficiency that causes permanent cognitive impairment

- Frequently underdiagnosed.
- Symptoms.
  - Fixed upward gaze.
  - Alcoholic neuropathy.
  - "Stocking-glove" paresthesia
  - Autonomic instability.
- Delirium encephalopathy.

Medical Treatment of Alcohol Withdrawal

While a full discussion of the pharmacological approach to alcohol withdrawal is beyond the scope of this chapter, a

basic approach to its treatment is given. The use of hydration, benzodiazepines, and, in some cases, neuroleptics is appropriate for the management of alcohol withdrawal syndrome (Table 45.3). The administration of a vitamin-mineral solution is indicated to counteract the effects of malnutrition that results from the alcohol itself and poor eating habits. Thiamine 100 mg administered intramuscularly or intravenously for 3 days before switching to oral administration for the duration of treatment will prevent the development of Korsakoff syndrome and alcoholic dementia. A daily oral dose of folate 1 mg should also be given throughout the course of treatment. In cases of mild withdrawal, hydration alone may be sufficient. Benzodiazepines (lorazepam, midazolam, diazepam, and chlordiazepoxide) are the drugs of choice for the management of alcohol withdrawal because of their sedative effects (Table 45.4) [65, 66]. Careful consideration must be given to route, absorption, potency, and dose of benzodiazepine prescribed. Dose should be based upon estimated alcohol consumption and the type of detoxification setting (see below). Insufficient administration of benzodiazepines (too low dose or too rapid taper) may allow the progression of withdrawal to a state of delirium tremens. The development of seizures is life-threatening, and they may repeatedly recur in the patient while unconscious. The nonbenzodiazepine anticonvulsants are not prescribed prophylactically. In cases of severe withdrawal and confusion, neuroleptics (i.e., haloperidol 0.5–5.0 mg IV every 8 h) are added to the treatment regimen. Commonly, alcoholic patients report to the hospital either intoxicated or in the early stages of withdrawal. From a surgical perspective, serious complications can arise from the presence of alcohol withdrawal, and its acute management is the primary treatment goal. Unfortunately, clinicians are frequently provided insufficient lead time to properly detoxify the patient prior to surgery (typically less than 24 h), and the patient is at an increased risk for the postoperative development of organic mental disorders, seizure, and delirium tremens. Since alcoholic cancer patients are already at high risk for delirium postoperatively due to poor nutrition, prior head trauma, and brain injury from excessive alcohol consumption, the development of seizures and delirium tremens adds to the risk of fatality. It is important to note that since it is desirable for the patient to be alert postoperatively for ambulation and use of pulmonary toilet, the amount of sedation required for detoxification is much lower than the desired level of sedation in a nonsurgical alcoholic patient.

Table 45.3 Guidelines for the treatment of alcohol withdrawal

Continual close monitoring of withdrawal status
Utilization of benzodiazepines
Taper dose slowly (generally not by more than 25% per 24-h period)
Administration of thiamine 100 mg IM or IV qid
Administration of folate 1 mg po qid
Monitor for signs of the potential onset of delirium tremens
Consideration should be given to a loading dose of phenytoin for patients with a history of withdrawal seizures or for patients in whom seizures are likely (i.e., patients with brain metastases)

Table 45.4 Types and characteristics of benzodiazepines for treatment of alcohol withdrawal

Drug	Dose	Duration of action	Half-life (h)
Chlordiazepoxide	25–100 mg every 3 h IV	Short	5–30
Diazepam	10–20 mg every 1–4 h IV	Short	20–100
Lorazepam	1–2 mg every 1–4 h IV	Intermediate	10–20
Midazolam	1–5 mg every 1–2 h IV	Very short	1–4

Considering the Therapeutic Impact of Tolerance

Patients who are active substance abusers may be tolerant to drugs administered for therapy, making pain management more difficult. The magnitude of this tolerance is never known. Therefore, it is best to begin with a conservative dose of therapeutic drug and then rapidly titrate the dose, with frequent reassessments, until the patient is comfortable [40, 41, 54]. Cancer patients and those with progressive disease can be treated with gradually increasing doses, and opioids can still be titrated to effect or toxicity with no arbitrary number of milligrams constituting a limit. Tolerance to a variety of opioid effects can be reliably observed in animal models [67], and tolerance to non-analgesic effects, such as respiratory depression and cognitive impairment [68], occurs regularly in the clinical setting. However, analgesic tolerance does not appear to routinely interfere with the clinical efficacy of opioid drugs.

Psychopharmacology Approaches

Disulfiram (Antabuse) is a pharmacological agent that has been approved by the Food and Drug Administration (FDA) since 1951 for the treatment of alcoholism. Antabuse serves as a deterrent by inducing an unpleasant physical state characterized by nausea or vomiting when alcohol is consumed, thus ideally leading to alcohol cessation [69]. The practicality and effectiveness of Antabuse is questionable however, since its use has been limited by difficulties with patient adherence for continued use of the drug [70].

There have been a number of studies shedding light on subgroups of patients who have been shown to benefit the most from treatment with Antabuse. The findings have shown that patients with the following characteristics generally

experience the most long-term benefits from Antabuse: (1) older than 40 years of age, (2) longer drinking histories, (3) socially stable, (4) highly motivated, (5) prior attendance of Alcoholics Anonymous, (6) cognitively intact, and (7) able to maintain and tolerate dependent or treatment relationships [71–73]. Further research is needed to ascertain what factors and patient characteristics will increase the likelihood of successful treatment. A greater understanding has the potential to significantly enhance clinicians' ability to select those patients who will experience optimal effectiveness.

Methadone Maintenance

Methadone maintenance therapy (MMT) is superior to illegal heroin use, in part, because the extreme highs and lows felt by heroin users (related to the waxing and waning of serum heroin levels) are avoided by the long-acting properties of methadone. The term "agonist blockade" was coined to describe the phenomenon of significantly limited or blunted effects after administration of "usual" doses of mu-opioid agonists to subjects on high-dose methadone (e.g., 80–120 mg/day).

In humans, all opioids suppress the hypothalamic-pituitary-adrenal (HPA) axis when given acutely, and this effect persists during chronic, intermittent exposure to short-acting opioids during chronic cycles of heroin addiction [74].

The endogenous mu-opioid receptor-mediated opioid system in humans appears to constitutively provide tonic inhibition of the HPA axis [74, 75]. Thus, administration of mu-opioid receptor antagonists to healthy human volunteers leads to activation of the HPA axis [75–79]. Similarly, the HPA axis is activated in opioid withdrawal (for which clonidine may be helpful [62]), or with administration of mu-opioid receptor antagonists to opioid-dependent individuals, or during acute cocaine or alcohol consumption [75, 78].

Kreek and colleagues [80] proposed that suppression of the HPA axis through administration of intermittent or binge-type short-acting opioids (e.g., heroin) and then with repeated alternating short cycling of suppression (e.g., with heroin administration), followed by activation (e.g., with heroin withdrawal [i.e., just before next dose]), may lead to and/or exacerbate atypical responsivity to stress/stressors, as well as addictive-type behavior (with resultant self-administration/relapse). Adequate methadone maintenance treatment permits normalization of the HPA axis—including response to a chemically induced stress of metyrapone challenge [81, 82]. In an optimal situation, stabilized methadone-maintained former heroin addicts treated in high-quality methadone maintenance treatment programs (e.g., associated with psychosocial interventions) with effective methadone doses experience the following: markedly reduced drug craving; reduced or eliminated heroin use; improved or normalized stress-responsive hypothalamic-pituitary-adrenal axis; and reproductive, gastrointestinal, and immunologic functions with relatively normal responses to acute pain [83, 84].

Buprenorphine and Naltrexone

Two other therapies used in the medication-assisted treatment (MAT) of those with opioid addiction and alcoholism are not without their complexities if they are to be used in people with cancer.

Buprenorphine is a partial opioid agonist that has significantly advanced MAT for opioid addiction on an international level. Available as a pill, sublingual film (with and without naltrexone), and as an implant for addiction treatment, its use in people with cancer can complicate the treatment of pain in the setting of disease progression and require dose escalation that could "bump up against" the drug's ceiling effect or in the treatment of acute pain requiring the use of a pure mu-agonist. However, there are also reports of the successful use of oral and transdermal buprenorphine for chronic and breakthrough cancer pain in nonaddicts [85]. If a person with cancer also has a history of opioid addiction and is to be managed with continuation of their buprenorphine treatment, consultation should be sought from an addiction medicine expert (who also has the appropriate certification to prescribe it where necessary). Options for managing pain exacerbations may include increasing the total daily dose and dividing the buprenorphine dose into 6- to 8-hour intervals, adding and titrating a short-acting and potent mu-agonist such as fentanyl, or discontinuing and switching buprenorphine to a full mu-opioid agonist. Emerging evidence supports that patients with opioid use disorders continue with buprenorphine treatment while the acute pain is being managed [86].

The oral opioid antagonist naltrexone is used to treat alcohol cravings and opioid addiction and is also available as a monthly depot injection for addiction treatment. While ultralow-dose naltrexone has been used to augment opioids for cancer-related pain and for the treatment of side effects such as constipation, little has been written about the use of this therapy for addiction treatment in people with cancer. While one can imagine antagonist therapy having a role in, for example, people surviving cancer who struggle with addiction (and in whom pain severe enough to require opioids is not part of the clinical picture) and in those with pain and with active disease, its role is limited. There is a paucity of data and direct clinical experience on which specific recommendations might be made. These medications can cause difficulties for the ED professionals as they might, for instance, need to intervene for acute pain in the ED setting,

the management of which is complex in persons on antagonist therapy.

Selecting Appropriate Drugs and Route of Administration for the Symptom and Setting

The use of long-acting analgesics in sufficient amounts may help to minimize the number of rescue doses needed, lessen cravings, and decrease the risk of abuse of prescribed medications, given the possible difficulty of using short-acting formulations in patients with substance abuse histories. Rather than being overly concerned regarding the choice of drug or route of administration, the prescription of opioids and other potentially abusable drugs should be carried out with limits and guidelines [21–23].

Many clinicians now respond to particularly high-opioid-dose requirements with rotation to another opioid. This practice capitalizes on incomplete cross-tolerance, or the unique pharmacology of methadone in particular, to bring doses down while maintaining or improving efficacy and changing the balance of efficacy to toxicity [87, 88]. Some clinicians set arbitrary dose limits for the various opioids. Others stop using certain opioids they perceive as of higher risk or street value. Still others became so disillusioned as to stop using opioids altogether.

Recognizing Specific Drug Abuse Behaviors

In an effort to monitor the development of aberrant drug-taking behaviors, all patients who are prescribed potentially abusable drugs must be evaluated over time. This is particularly true for those patients with a remote or current history of drug abuse, including alcohol abuse. Should a high level of concern exist regarding such behaviors, frequent visits and regular assessments of significant others who can contribute information regarding the patient's drug use may be required. To promote early recognition of aberrant drug-related behaviors, it may also be necessary to have patients with histories of recent active abuse to submit urine specimens for regular screening of illicit, or licit but non-prescribed, drugs. When informing the patient of this approach, explain that it is a method of monitoring that helps the clinician keep the patient safe and provides a foundation for aggressive symptom-oriented treatment, thus enhancing the therapeutic alliance with the patient [21–23].

Using Nondrug Approaches as Appropriate

The most effective psychotherapeutic treatment approach with medically ill people appears to be one that focuses on the development of effective coping skills, relapse prevention, and, most importantly, treatment compliance. Alcohol or the specific substance being abused represents one of the dependent patient's primary, albeit maladaptive, coping tools. As a result, the improvement of coping skills in these individuals is critical. When compounded with the stress associated with cancer, substance abuse cessation can be overwhelming and contribute to noncompliance and discontinuation of treatment. Teaching specific, illness-related coping methods with an emphasis upon containing episodes of consumption is essential. Further, the recognition and treatment of anxiety and depression may decrease the patients' need and desire for alcohol or substances. As an alternative to the abstinence approach, a harm reduction with crisis intervention as a central component should be utilized. The fundamental aims of this approach are enhancement of social support, maximization of treatment compliance, and containing harm associated with episodic relapses. Further, minimizing the frequency and intensity of the patients' use and consumption is the broad goal of treatment. Therefore, further damage to the patient will be reduced as well as the facilitation of treatment compliance.

Other psychotherapeutic approaches beneficial for this population are support groups and 12-step programs. The problem lies in that traditional 12-step groups are based on an abstinence-only policy. This poses a problem for patients who are being treated with opioids for pain-related syndromes. More recently, support groups have been tailored for this specific population.

Many nondrug approaches exist to assist patients in coping with chronic pain in advanced illness. Such educational interventions may include relaxation techniques, ways of thinking of and describing the experience of pain, and methods of communicating physical and emotional distress to staff members. Although nondrug interventions are adjuvants to management, they should not be perceived as substitutes for drugs targeting pain or other physical or psychological symptoms [21–23].

Developing the Treatment Plan

Inpatient Management Plan

In designing the inpatient management of an actively abusing patient with advanced illness, it is helpful to use structured treatment guidelines. Although the applicability of these guidelines may vary from setting to setting, they provide a set of strategies that can ensure the safety of the patient and staff, control possible manipulative behaviors, allow for supervision of illicit drug use, enhance appropriate use of medications for pain and symptom control, and communicate an understanding of pain and substance abuse management [21–23].

Under certain circumstances, such as actively abusing patients who are scheduled for surgery, patients should be admitted several days in advance, when possible, to allow for stabilization of the drug regimen. This time can also be used to avoid withdrawal and to provide an opportunity to assess whether modifications of an established plan are necessary [21, 22].

Once established, the structured treatment plan for the management of active abuse must proceed conscientiously. In an effort to assess and manage symptoms, frequent visits are usually necessary. It is also important to avoid drug withdrawal, and, to the extent possible, prescribed drugs for symptom control should be administered on a regularly scheduled basis. This helps to eliminate repetitive encounters with staff that center on the desire to obtain drugs [21–23].

Treatment management plans must be designed to represent the clinician's assessment of the severity of drug abuse. Open and honest communication between clinician and patient to stress that the guidelines were established in the best interest of the patient is often helpful. However, in cases where patients are unable to follow these guidelines despite repeated interventions from the staff, discharge should be considered. Clinicians should discuss this decision for patient discharge with the staff and administration while considering the ethical and legal ramifications of this action [21–23].

Outpatient Management Plan

Alternative guidelines may be used in the management of the actively abusing patient with advanced illness who is being treated on an outpatient basis. In some instances, the treatment plan can be coordinated with referral to a drug rehabilitation program. However, patients who are facing end-of-life issues may have difficulty participating in such programs. Using the following approaches may be helpful for managing the complex and more difficult-to-control aspects of care.

Case Study

*A 36-year-old white male with stage IV lung cancer (Pancoast tumor) that was locally advanced and widely metastatic presented late after a 35-lb weight loss. His sister had died of the same disease at age 35, and he had a history of significant substance abuse and drug dealing. The patient complained of out-of-control pain and lack of willingness of any local providers to prescribe pain medication. The patient was inflexible about acceptance of any other treatments (*i.e., *nerve block, epidural) other than OxyContin™. The patient's pain was 10/10 from brachial plexopathy with mixed neuropathic/somatic/visceral components.*

Patient was titrated to effect over time. The maximum dose reached 800 mg bid at the time of death with 100 mg liquid MS04 q1h rescues. Although the patient was dying, structured management was required because of his history. The structured management plan was as follows: hospice nurses delivered one-day supply, unscheduled visits for pill counts, urine screens, and a reliable family member was identified to lock up pain medication supply.

The patient settled down and with renewed trust was willing to add nortriptyline, which helped with neuropathic pain, as well as steroids for nausea, cachexia, and fatigue.

Recommendations for Prescribing

Patients who are actively abusing must be seen weekly to build a good rapport with staff and afford evaluation of symptom control and addiction-related concerns. Frequent visits allow the opportunity to prescribe small quantities of drugs, which may decrease the temptation to divert and provide a motive for not missing appointments [21–23].

Procedures for prescription loss or replacement should be explicitly explained to the patient, with the stipulation that no renewals will be given if appointments are missed. The patient should also be informed that any dose changes require prior communication with the clinician. Additionally, clinicians who are covering for the primary care provider must be advised of the guidelines that have been established for each patient with a substance abuse history to avoid conflict and disruption of the treatment plan [21–23].

Twelve-Step Programs

Depending on the patient's stage of advanced illness and functional status, the clinician may consider referring the patient to a 12-step program with the stipulation that attendance be documented for ongoing prescription purposes. If the patient has one, the clinician may contact the patient's sponsor, depending on the stage of illness and individual capabilities, in an effort to disclose the patient's illness, and that medication is required in the treatment of the illness. This contact will also help decrease the risk of stigmatizing the patient as being noncompliant with the ideals of the 12-step program [21–23]. If the patient is unable to participate in a 12-step program, other psychosocial and/or spiritual team members can provide care that supports sobriety.

Urine Drug Testing and Prescription Drug Monitoring Programs

One of the most commonly utilized risk management tools in chronic non-cancer pain management and adherence monitoring/sobriety in addiction treatment is urine drug testing (UDT). Depending on the method employed, UDT can be used to gauge whether the patient is adherent to their prescribed medication, whether or not they are also taking non-prescribed licit medications, and/or whether they are using illicit drugs and alcohol [89]. Indeed, one study in which primary care doctors were taught to employ a "menu" of risk management techniques (including UDT) and then studied over time to examine their use of them found that UDT was the most commonly retained practice element on 6-month follow-up [90].

UDT is underutilized in the management of cancer-related pain with opioids [91]. Perhaps oncologic ED professionals, due to their lack of familiarity with the evolution in methods and mind-set that had occurred in the laboratory and clinic in the last decade, think of UDT in only its forensic incarnation. In that view, UDT is a means out of finding if "bad people" are "doing bad things," as seen in a prior chart review study [92]. Thus, because of this stigma, they are fearful that introducing UDT to their patients and integrating it into patient management will be offensive, and they may lack an approach for discussing it in a non-shaming manner with their patients. However, recent research in addiction treatment suggests that UDT can be utilized with patients in a non-stigmatizing manner when clinicians take the perspective that patients with substance abuse problems deserve help, and UDT is seen as a supportive tool for the patient's benefit [93]. The forensic method, from which more modern clinical testing sprung, tends to rely on immunoassay (IA) testing which offers fast but only class-level (not drug-specific) results with high cutoffs. It is meant to detect recent use of classes of drugs that would impair, for example, a truck driver from driving. Cutoffs are high because of the legal and other consequences that could follow and to avoid falsely accusing people. In recent years, gas chromatography and liquid chromatography with mass spectrometry are capable of giving highly accurate drug-specific results and return them in a timely fashion (1–2 days as opposed to 10 days–2 weeks). Such results can be used to determine whether a patient is misusing a range of drugs or alcohol and gauge their adherence with specific medication and controlled substance regimens. More data is needed in this area [91], but the use of UDT for those with pain and/or substance use disorder is well documented [94–98].

Oncologic personnel in the ED should routinely access prescription drug monitoring program (PDMP) prior to prescribing a scheduled medication. Checking PDMPs can identify patients who may be receiving overlapping prescriptions, obtaining prescriptions from multiple prescribers, or misusing their scheduled medications [99]. A point that is often overlooked is that patients in oncologic settings can benefit from the clinician's use of PDMPs as much as in any chronic pain setting. Patients being treated for cancer are more likely than with some other chronic pain conditions to have multiple prescribers. Coordinating care can be a challenge, and patients are at risk for being overmedicated. Although not intended for patients with cancer, clinicians should be aware of the Center for Disease Control and Prevention guidelines [100], which recommend checking the PDMP prior to initiating a scheduled medication and at least every 3 months thereafter.

Family Sessions and Meetings

The clinician, in an effort to increase support and function, should involve family members and friends in the treatment plan. These meetings allow the clinician and other team members to become familiar with the family and additionally help the team identify family members who are using illicit drugs. Offering referral of these identified family members to drug treatment can be portrayed as a method of gathering support for the patient. The patient should also be prepared to cope with family members or friends who may attempt to buy or sell the patient's medications. These meetings will also assist the team in identifying dependable individuals who can serve as a source of strength and support for the patient during treatment [21–23]. These published guidelines generally advocate an approach to UDT based on risk stratification (i.e., frequency of testing and choice of methods are aimed at matching the approach to the level of risk of abuse, addiction, and diversion in an individualized way to each patient). Such an approach seeks to maximize the benefit of testing while also managing cost. As oncologic professionals learn to integrate UDT into treatment of the person with cancer and addiction or the management of chronic opioid therapy, there is no reason to think that the adaptation of a similar approach might not be a reasonable way to proceed.

Conclusion

Treating oncologic patients with chronic pain and substance use disorders is both complicated and challenging, as each can significantly complicate the other. Whether our patients respond to cancer treatments or have life-limiting disease, we can no longer justify high-dose opioid therapy in a vacuum without trying to assess and manage addiction and abuse behaviors. Using a treatment plan that involves a team

approach to recognize and respond to these complex needs is the optimum treatment strategy. While pain management may remain challenging even when all treatment plan procedures are implemented, the healthcare team's goal should be providing the highest level of pain management for all patients with substance use disorders.

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Radiology

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Jihoon Lim, Keith D. Herr, and Tarek N. Hanna

Introduction

Oncologic emergencies encompass a wide spectrum of pathology and can affect any organ system. These can be divided into metabolic, hematologic, and structural emergencies [1]. Metabolic and hematologic conditions are frequently diagnosed based on clinical and laboratory findings, often with only incidental imaging support. Structural emergencies are those arising from mass effect, tissue infiltration, tumor hemorrhage, vascular invasion with resulting occlusion or hemorrhage, and organ drainage pathway obstruction. Diagnostic imaging can also provide a "road map" for subsequent image-guided interventional and noninvasive therapies.

Imaging Modalities

There is a wide array of diagnostic imaging options available for evaluating oncologic emergencies. Selecting the appropriate imaging modality requires consideration of availability, speed, patient-specific factors, and anticipated diagnostic yield.

Plain Radiography Rapid, universally available, low-cost screening modality. Core utility is for osseous and pulmonary evaluation and to screen for intestinal obstruction and pneumoperitoneum. Particularly useful in trauma to the appendicular skeleton. Less sensitive in the diagnosis of axial and spinal trauma, although still used as a screening tool.

Computed Tomography (CT) Rapid and highly available. Mainstay in the emergent evaluation of the head, neck, chest, abdomen, and pelvis. Modern multidetector CT technology allows for thin X-ray beam collimation to 0.625 mm, allowing for isotropic image acquisition and post-processing capabilities, including orthogonal and curved planar reformations, as well as 3D surface rendering [2].

The diagnostic value of CT derives from its ability to discriminate tissues based on physical density, measured in Hounsfield units (HU) and displayed in gray scale on a picturing and archiving communication system (PACS) workstation. By convention, water has a density of 0 HU and appears intermediate in gray scale. Air has a density of approximately −1000 HU and appears relatively dark (hypodense or hypoattenuating). Bone and calcium have densities in the range of +1000 HU and appear relatively bright (hyperdense or hyperattenuating). Intravascular or unclotted extravascular blood, for example, has a density of around 30–45 HU but increases in attenuation to 45–70 HU as clot develops [3]. Administration of iodine-based nonionic intravenous (IV) contrast increases soft tissue and vascular conspicuity, further improving diagnostic yield. Most malignancies display predictable enhancement characteristics, and the use of IV contrast often permits accurate diagnosis. In oncologic emergencies, routine use of IV contrast is suggested for the neck, chest, abdomen, and pelvis, primarily for soft tissue evaluation. However, ED personnel evaluating female patients with pelvic pain should refrain from ordering an abdominal or pelvic CT scan without first consulting the gynecologic oncologic team, as such scans are often of low yield [4]. For the evaluation of osseous pathology, IV contrast is not usually necessary. Most intracranial emergencies are imaged with head CT without IV contrast, as opacified intracranial vessels may obscure extra-axial hemorrhage. Optimizing arterial or venous enhancement by adjusting the timing of image acquisition allows for an assessment of vascular abnormalities, such as dural venous sinus or cortical vein thrombosis (on CT venogram) or vasospasm (on CT angiogram). Recent advances in CT technology have led to increased utilization of dual-energy CT in clinical practice. Dual-energy CT assesses attenuation at two

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different energy levels, usually at low energy (80–100 kVp) and high energy (140–150 kVp). Based on atomic interactions between imaged tissue and X-rays at low and high energy levels, it is often possible to determine the type of material in each voxel, improving tissue contrast beyond conventional single-energy CT [5]. This approach may help to distinguish between traumatic and pathologic bone fractures [6].

Magnetic Resonance Imaging (MRI) May not be accessible after-hours at many centers. MRI requires a greater degree of patient stability and compliance than does CT and entails longer imaging times. Due to the powerful magnet used in MRI, ferromagnetic metal-containing objects inside the body can pose significant risk to the patient, as they may heat up or migrate during the exam. As a result, the presence of ferromagnetic metal-containing devices within the patient is an absolute contraindication for MRI. In addition, implanted cardiac devices may malfunction in a strong magnet and are often contraindicated for MRI. The core utility for MRI in the emergent setting is for intracranial (e.g., acute stroke, tumor burden, dural venous sinus thrombosis) and spine (e.g., cord compression, cord edema, epidural tumor, and osseous involvement) evaluation. Gadolinium-based IV contrast aids in quantifying the extent of malignant disease and can potentially characterize soft tissue tumors. As with CT, IV contrast is typically not essential for osseous evaluation but may be helpful in characterizing bone invasion of a soft tissue tumor. Commonly performed MR imaging sequences for the brain include T1-weighted (T1), T2-weighted (T2), fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and gradient echo (GRE). For spinal imaging, typical sequences are acquired in the sagittal plane and include T1, T2, and either T2 fat-saturated or short-tau inversion recovery (STIR) images, as well as GRE and postcontrast sequences. Axial image sequences for the spine are institution-dependent but typically include T1 and T2 images. If IV contrast is administered, postcontrast T1 images are obtained using fat-saturation techniques. Signal from fat is bright (hyperintense) on MRI. When background fat signal is suppressed, it appears dark (hypointense), increasing the conspicuity of contrast-enhanced malignant tissue. MRI imaging of the long bones often employs proton density (PD) sequences as an alternative to fat-saturated T2 images. Signal from blood is hypointense on GRE and demonstrates variable signal on T1 and T2 images depending on time course. As with CT angiography (CTA) or venography (CTV), MR angiography (MRA) and venography (MRV) can be used to assess for vascular pathology, although IV contrast is not always necessary.

Ultrasonography (US) Rapid, universally available, mobile, and accessible for clinician bedside usage. This soundwave-based modality is limited by image degradation that occurs at tissue interfaces with bone or air. Doppler US is ideally suited for the assessment of blood vessels and soft tissue vascularity and highly useful in procedural guidance owing to its portability and absence of radiation. US is a good tool for extremity soft tissue disease, ascites, pleural effusions, vessel patency, and biliary pathology. Some drawbacks of ultrasound include susceptibility to artifacts and dependence on operator technique and patient cooperation. (A separate chapter on emergency ultrasound follows.)

Nuclear Medicine In the emergent setting, ventilation-perfusion (V/Q) imaging may be used to evaluate for pulmonary embolism. V/Q studies are reserved for patients with contraindications to CT pulmonary angiogram (CTPA), such as a history of significant adverse reaction to iodinated IV contrast agents or renal insufficiency. A tagged red blood cell scan (erythrocytes labeled with technetium-99^{m}) may be used to localize the general area of gastrointestinal bleeding to guide subsequent treatment. Positron emission tomography (PET) has minimal value in the emergent oncologic patient due to increased patient preparation requirements, lengthy acquisition time, and limited availability. Other nuclear medicine exams have established utility in imaging oncologic patients (e.g., whole-body bone scintigraphy); however, these are infrequently used in the emergent setting.

Fluoroscopy Useful for esophagrams and to provide procedural guidance for lumbar puncture, myelogram injection, joint aspiration, and tube/drain placement.

Interventional Radiology Interventional procedures can provide further diagnostic information, as well as guide therapies in the acute setting, most commonly with the use of conventional catheter angiography, embolization for acute hemorrhage, and tube or drain placement for relieving obstruction or abscess drainage.

Radiologic Evaluation of Oncologic Emergencies

The following is a concise review of the imaging evaluation of oncologic emergencies, highlighting important imaging characteristics of key malignancy-related conditions across a range of organ systems to serve primarily as a resource for clinicians involved in cancer care and for radiology trainees, who will invariably encounter oncologic emergencies during training and beyond.

Neurologic Emergencies

Intracranial Mass Effect, Edema, and Hemorrhage Fundamentally, malignant tumors are space-occupying masses that compete with normal anatomical structures for limited space in the brain and spinal canal. Intracranial mass effect derives from a combination of tumor volume and peritumoral edema, which together are responsible for causing various cerebral herniation patterns and hydrocephalus. Effective tumor volume can change rapidly as a consequence of necrosis, hemorrhage, and cyst formation, which contribute to mass effect (Fig. 46.1).

On unenhanced head CT, the appearance of malignant tissue is variable, depending on its histological composition. Generally, malignant tumors are slightly hyperdense relative to white matter, and hemorrhagic or melanin-containing components are considerably denser (e.g., malignant melanoma). Cystic and necrotic components generally measure near-water attenuation depending on the presence of cellular debris or blood products. Perilesional edema results in relative hypodensity of the surrounding brain parenchyma. Especially on unenhanced CT, the presence of edema and associated mass effect may be the only indication of underlying malignancy, and further evaluation with a contrast-enhanced study, ideally MRI, is indicated. Edema from malignancy is a reactive process, and the amount of edema is proportional to tumor size and rate of growth. Accordingly, a small but rapidly growing mass may present as precipitously as a larger but more indolent mass. Tumor cell lysis and treatment-related neurotoxicity represent important additional sources of edema and mass effect, which can be antici-

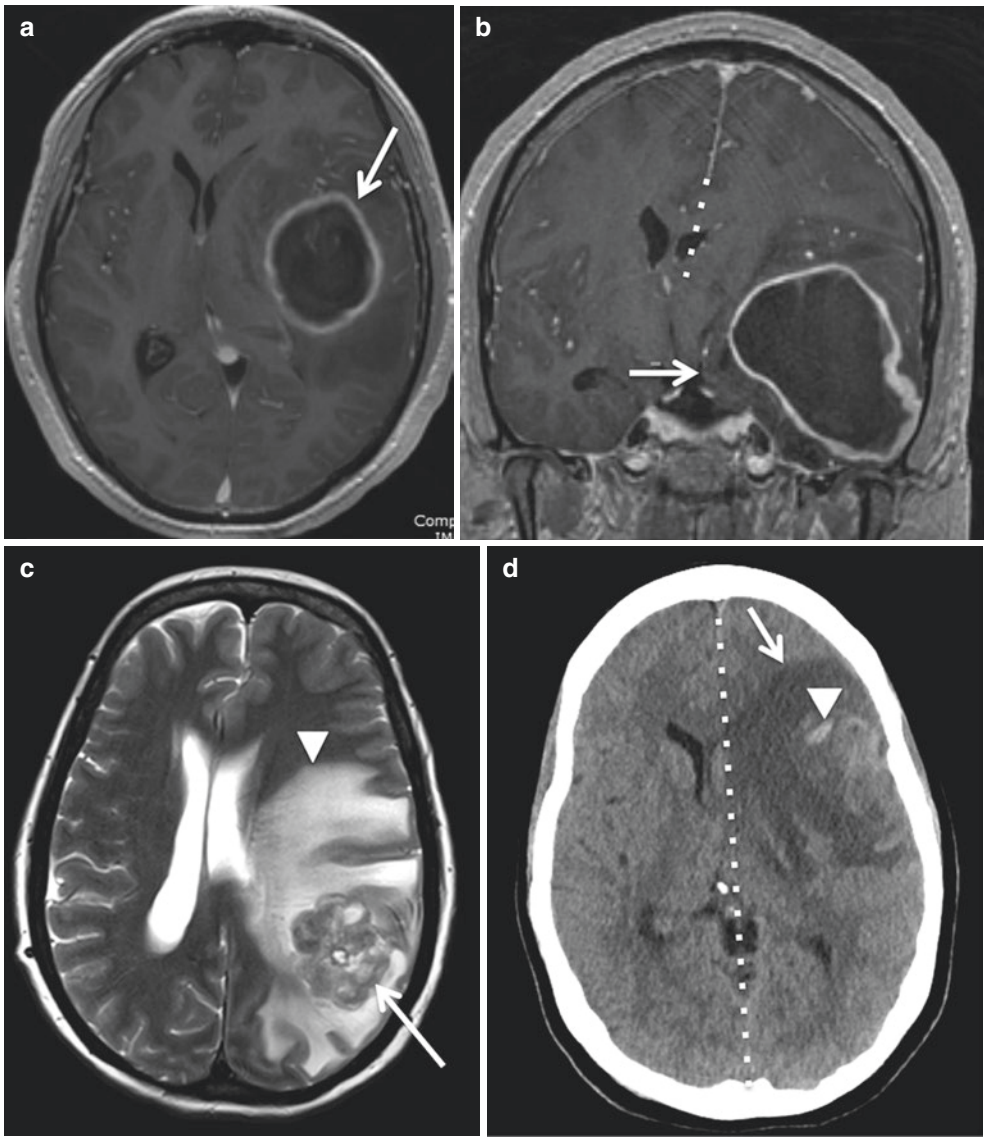

Fig. 46.1 Intracranial mass effect. (**a**) Axial postcontrast T1 brain MR image demonstrates a rim-enhancing intraparenchymal cavitary metastatic mass (*arrow*). (**b**) Coronal contrast-enhanced T1 MR image in the same patient demonstrates left-to-right midline shift (*dotted line*), compatible with subfalcine herniation. Uncal herniation is also shown by an arrow on image **b**. (**c**) T2 axial brain MR image depicts marked T2-hyperintense edema surrounding a cystic intraparenchymal metastatic lesion in the left parietal lobe (*arrow*). Note extent of edema beyond the actual mass (*arrowhead*). (**d**) Unenhanced head CT image demonstrates a left frontal lobe mass with marked surrounding hypodense edema (*arrow*) and local sulcal effacement and left-to-right midline shift (*dotted line*). There is small-volume intra-tumoral hemorrhage (*arrowhead*), which may have caused this patient's acute presentation

pated and prospectively managed with systemic corticosteroid administration.

Intracranial herniation resulting from mass effect can be classified as subfalcine, transtentorial, transalar, and tonsillar [7]. Transtentorial herniation can be further characterized as ascending (originating from the posterior fossa), descending (cerebral hemispheres), or uncal (temporal lobes), depending on the location of the tumor [1]. Ascending transalar herniation results from middle cranial fossa mass effect and causes superior and anterior temporal lobe displacement across the sphenoid ridge [7]. Descending transalar herniation results from frontal lobe mass effect and causes posterior and inferior displacement across the sphenoid wing [7]. Masses located in tightly confined structures, such as the posterior fossa, can result in the rapid development of clinically significant herniation.

Patients with hypervascular metastases, such as renal cell carcinoma, melanoma, thyroid cancer, and choriocarcinoma, are at highest risk for both intra-axial (within the brain substance) and extra-axial (within the epidural, subdural, or subarachnoid space) hemorrhage [8, 9]. Intracranial hemorrhage can also result from acute disseminated intravascular coagulation (DIC), to which patients with hematologic tumors are particularly predisposed [10]. Regardless of cause, intra-axial hemorrhage appears as a hyperdense mass with a variable degree of circumferential edema on unenhanced head CT. Hyperdensity in the subarachnoid, subdural, or epidural spaces indicates extra-axial hemorrhage. Contrast-enhanced brain MRI is essential for further characterizing the underlying malignancy.

Hydrocephalus Hydrocephalus is classified as noncommunicating (obstructive) and communicating (nonobstructive). Noncommunicating hydrocephalus results from obstruction of CSF flow, while communicating hydrocephalus is the result of excess CSF production or decreased resorption at the arachnoid villi. The foramen of Monro, aqueduct of Sylvius, and the fourth ventricle are anatomically prone to obstruction by the presence of an adjacent primary or metastatic mass [9]. Specifically, pineal metastases or primary pineal neoplasms have a particular association with hydrocephalus given the location of the gland within the narrow channel between the third ventricle and the superior cerebellar cistern [11]. The primary feature of communicating (nonobstructive) hydrocephalus on unenhanced CT is global ventricular enlargement. In noncommunicating (obstructive) hydrocephalus, there is disproportionate enlargement of the lateral ventricles; the third ventricle may also be disproportionately enlarged depending on the anatomic level of obstruction. In acute hydrocephalus, increased ventricular pressure can result in transependymal CSF accumulation, resulting in a low-density appearance to the immediate periventricular white matter.

Leptomeningeal Metastatic Disease The pia and arachnoid mater are interconnected, thin, weblike tissue that envelops the brain parenchyma and together comprise the leptomeninges; leptomeningeal metastatic disease (also referred to as leptomeningeal carcinomatosis) is characterized by the deposition of tumor along these membranes. These tumoral cells can subsequently impede CSF resorption by obstructing the arachnoid villi, leading to communicating hydrocephalus [9]. Leptomeningeal metastatic disease portends a dim prognosis, with median survival in the range of 2–3 months [12]. It is important to note that up to 40% of patients with leptomeningeal metastatic disease may have normal unenhanced CT, and in an additional 25% of cases, leptomeningeal metastatic disease is indistinguishable from intraparenchymal disease [13]. Unenhanced MRI findings include high FLAIR signal within the cerebral sulci, cerebellar folia, and cisterns and communicating hydrocephalus [14]. Contrast-enhanced MRI findings include linear or nodular enhancement within the sulci, cisterns, and ventricles and along the cranial nerves [1]. The most common primary solid malignancies associated with leptomeningeal metastatic disease are breast and lung [13].

Dural Venous Sinus Thrombosis There are many benign causes of dural venous sinus thrombosis (DVST), including oral contraceptive use, pregnancy, thrombophilic disorders (such as factor V Leiden, protein C/S deficiency), recent immobilization, and infection, such as meningitis or mastoiditis [15]; however, patients with malignancy have a particularly elevated risk for developing DVST related to dehydration, chemotherapy effects, and hypercoagulable state [16]. Tumor involvement of the cranium or skull base, dura, or leptomeninges may result in local venous stasis secondary to mass effect on a dural venous sinus, representing an additional mechanism for DVST formation. Specific cancer chemotherapeutic agents that have known association with the development of DVST include asparaginase, cisplatin, and thalidomide [17].

Unenhanced head CT is often the initial imaging modality used to evaluate patients suspected of having DVST, who may present with signs and symptoms of increased intracranial pressure [17]. The classic unenhanced head CT finding in uncomplicated DVST is hyperdensity within the affected dural venous sinus, although this is not invariably present (Fig. 46.2). The superior sagittal and transverse sinuses are most frequently affected in DSVT [16]. The diagnosis is confirmed with CTV or MRV, both of which will depict an intraluminal filling defect within the affected sinus. CTV is faster and usually more accessible after-hours, while MRV is performed alongside MRI of the brain, providing a more sensitive assessment for early venous ischemia or congestion resulting from DVST. In cases of venous infarct, edema or

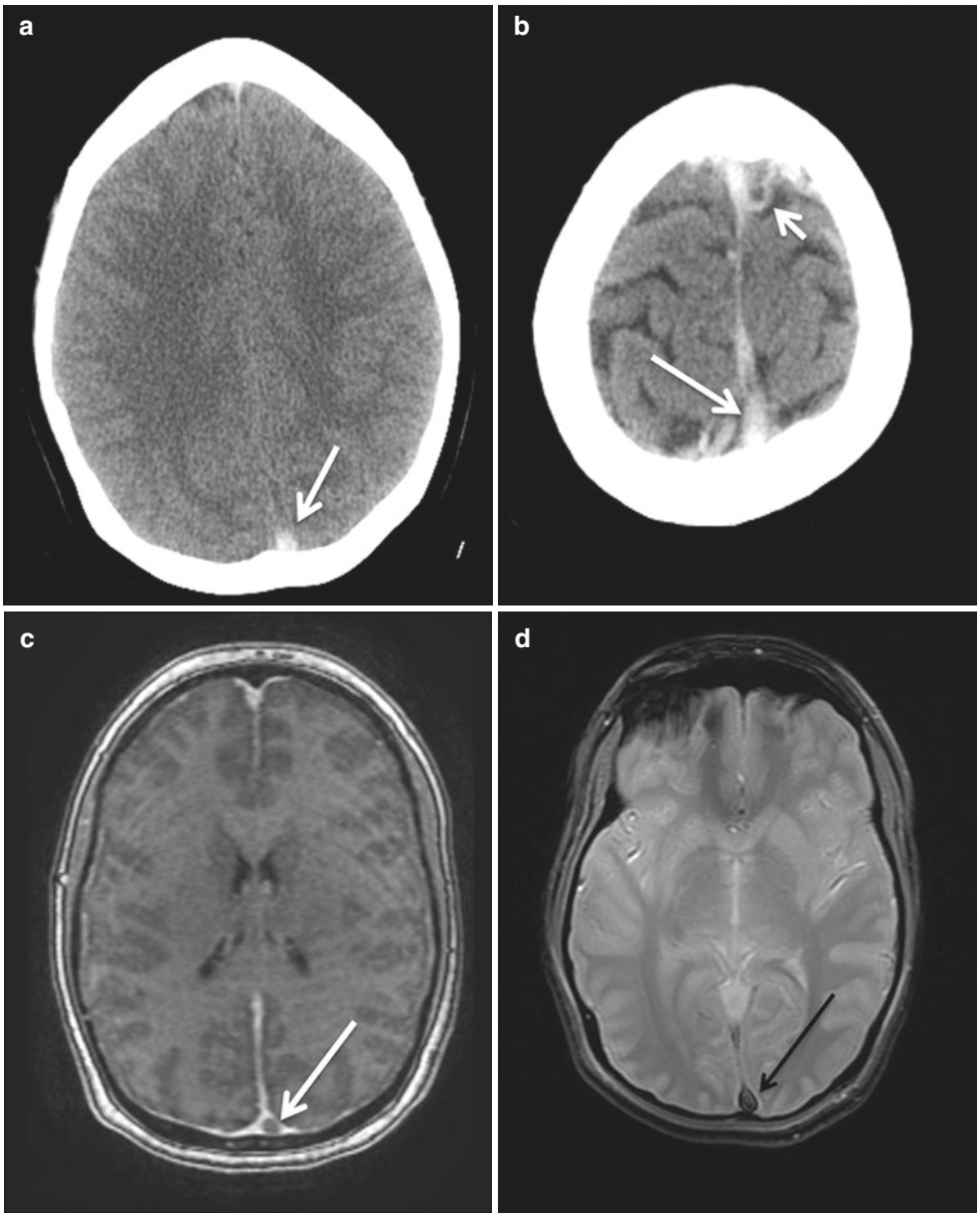

Fig. 46.2 Dural venous sinus thrombosis. (**a**) Axial unenhanced head CT image in a patient with lymphoma and headache demonstrates a hyperdense superior sagittal sinus (white *arrow*), suggesting superior sagittal sinus thrombosis. (**b**) A more superior unenhanced axial head CT image in the same patient near the vertex demonstrates continued superior sagittal sinus hyperdensity (*long arrow)* and multiple adjacent hyperdense cortical veins, suggesting thrombosis of these superficial veins as well (*short arrow*). (**c**) Postcontrast T1 axial brain MR image in the same patient illustrates a hypointense filling defect in the superior sagittal sinus, compatible with thrombus (*white arrow*). (**d**) Gradient echo axial brain MR image demonstrates "blooming" in the superior sagittal sinus, indicative of extracellular blood products (*black arrow*)

hemorrhage in a non-arterial distribution is common. Treatment of tumor-related DSVT is typically brain irradiation or chemotherapy, depending on tumor histology [10].

Stroke The hypercoagulable state of malignancy constitutes the primary risk factor for the development of cerebral vascular accidents (CVA) in oncologic patients [10]. As noted above, this population is at elevated risk for DVST, which can lead to ischemia and hemorrhagic infarction. Leptomeningeal infiltration of the Virchow-Robin perivascular spaces can result in arterial infarction secondary to thrombosis or vasospasm [10]. Additionally, arterial infarction can occur secondary to herniation as a consequence of compression of large arteries against rigid intracranial structures, such as the cerebral falx or tentorium. For instance, transfalcine herniation can result in anterior cerebral artery (ACA) compression and ipsilateral ACA-territory infarct [1, 8]. Similarly, transtentorial herniation can result in compression of the posterior cerebral artery (PCA) and therefore result in PCA-territory infarct [8]. Less commonly, transalar herniation can result in compression of the carotid terminus and lead to infarction in both the ACA and MCA territories.

Although the initial imaging evaluation of stroke patients regardless of cause is with unenhanced head CT, MRI provides optimal evaluation of tumor location and extent (including leptomeningeal metastatic disease) and is more sensitive in the identification of early ischemia as compared to CT. Areas of acute ischemia are markedly hyperintense on DWI and are typically associated with increased T2 signal.

Conventional MRI can provide an overall assessment of vessel caliber and enhancement, but dedicated MRA or MRV sequences provide better detail of arterial and venous pathology.

Spinal Pathology Spinal disease can be divided into pathology involving the osseous spine and that contained within the spinal canal (most commonly epidural or intramedullary involvement). Osseous spine disease is also addressed in the musculoskeletal subsection. Here, we focus primarily on epidural and intramedullary spinal disease, which can both present as oncologic emergencies. Metastatic disease of the spinal epidural space occurs in 5–10% of patients with cancer, most commonly from prostate, breast, and lung primaries [18]. When epidural tumor volume is advanced, it compresses the thecal sac and can result in malignant spinal cord compression (Fig. 46.3). In addition to metastatic disease, spinal cord compression can result from mass effect from primary bone tumors, osseous lymphoma, or multiple myeloma. Spinal epidural metastases localize to the thoracic region in 60% of cases and lumbosacral area in 30% of cases. Cervical spine involvement is less common [18].

Plain radiography is often the initial modality used in the evaluation of spinal cord compression, despite its poor predictive value in determining which patients will have spinal tumor involvement [19]. Vertebral body height loss secondary to pathologic compression is one of the most easily identifiable findings on plain radiography. Compression fractures resulting in loss of vertebral body height ≥50% is associated with spinal epidural disease in nearly 85% of cases [18]. Erosion of the osseous margins of the spine may be the earliest radiographic sign of intraspinal extension of disease, but this finding is not sensitive [20]. Vertebral pedicle erosion, in particular, may be the most specific finding of epidural disease [18]. CT is superior to plain radiography in accurately depicting bone erosion and assessing compression fractures. A further advantage of CT over plain radiography is that nonosseous disease can often be identified, although MRI is better suited for soft tissue pathology. CT can also be helpful in planning for interventional procedures or surgery.

MRI provides the most sensitive and specific evaluation of bone marrow pathology, epidural tumor and spinal cord compression, and intramedullary spinal disease. Spinal cord compression is discussed in detail in a separate chapter. Metastatic involvement of the spinal cord parenchyma is referred to as intramedullary spinal cord metastasis (ISCM) [18, 21]. Although ISCM has become much more frequently recognized in the era of MRI, spinal epidural disease is still nearly 20 times more common [18]. ISCM affects the cervical, thoracic, and lumbar cords equally and is most often solitary [18]. Bronchogenic carcinoma, particularly small cell carcinoma, accounts for the majority of cases (54%) [18]. MRI with IV contrast is necessary for the diagnosis of ISCM and can effectively discriminate spinal cord edema from enhancing tumor. Intravenous contrast also helps in differentiating tumor with surrounding edema from transverse myelitis.

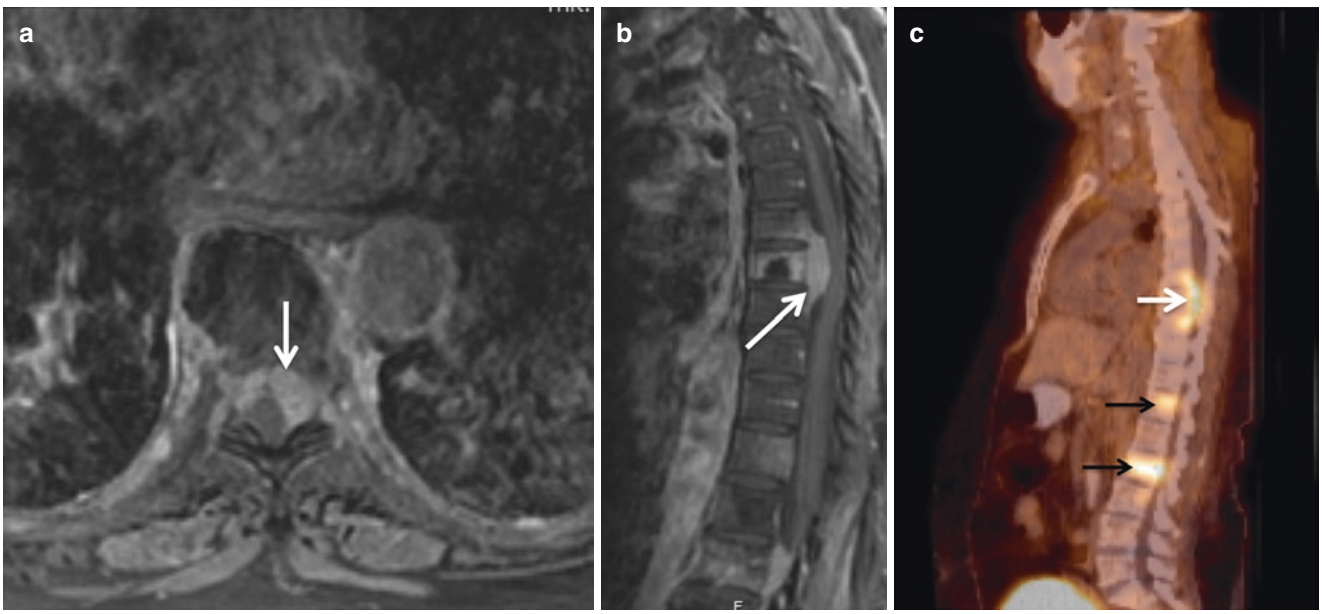

Fig. 46.3 Postcontrast axial T1 MR image (**a**) and sagittal postcontrast T1 MR image of the thoracic spine (**b**) depict an enhancing mass arising from the T7 vertebra and extending into the epidural space (*white arrows*). There is associated severe cord compression. A single fused sagittal FDG-PET/CT image of the entire spine (**c**) demonstrates robust metabolic activity in the tumor at the T7 vertebral level (*white arrow*) and at several other remote vertebral levels (*black arrows*)

Additional Acute Neurologic Complications of Malignancy Neurologic complications of cancer treatment include chemotherapy or brain irradiation-induced brain edema and attendant intracranial hypertension and opportunistic infection from systemic immunosuppression [8]. Infectious meningitis is often undetectable with unenhanced head CT; however, entities such as invasive fungal sinusitis or herpes encephalitis can be apparent on unenhanced head CT and be further characterized with brain MRI. Paraneoplastic limbic encephalitis, which can present with acute-onset confusion, short-term memory loss, hallucinations, and mood changes, is particularly difficult to diagnose clinically as it can be confused with primary psychiatric conditions. Furthermore, limbic encephalitis can have a similar imaging appearance to herpes encephalitis [8]. In 70–80% of patients with limbic encephalitis, MRI FLAIR or T2 sequences show hyperintense signal in one or both medial temporal lobes (Fig. 46.4) [22]. The tumors most frequently implicated are small cell lung cancer, testicular germ-cell neoplasms, thymoma, Hodgkin lymphoma, and teratoma [22].

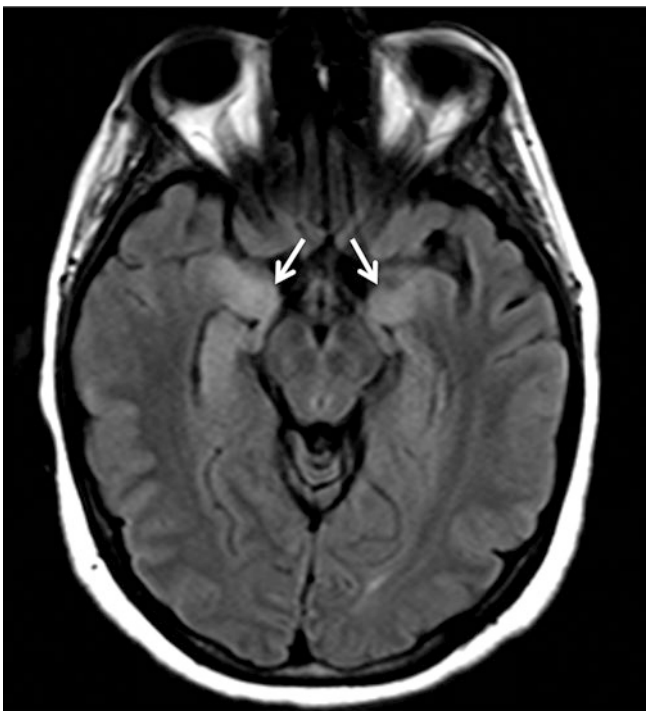

Fig. 46.4 Single FLAIR axial brain MR image in an emergency department patient with small cell lung cancer and altered mental status depicts bilateral medial temporal hyperintensity (*arrows*). Diagnosis of paraneoplastic limbic encephalitis was based on clinical and imaging characteristics

Chest Emergencies

Central Airway Obstruction Airway compromise necessitating palliative treatment occurs in 20–30% of patients with lung cancer over the course of their lifetime [23, 24]. Airway narrowing can result from intrinsic tracheobronchial disease, extraluminal compression by tumor, or a combination of both [2, 23]. Anatomical distortion of the airways as a result of surgery for lung cancer can also lead to airway compromise [23]. Chest radiography is often the initial imaging test in these patients and may reveal a mass involving the lung parenchyma, hilum, or mediastinum with associated post-obstructive atelectasis or pneumonia [2]. Tracheal deviation or airway narrowing may be present [25].

The imaging gold standard for the assessment of the central airway obstruction is contrast-enhanced CT chest and neck (above the thoracic inlet) (Fig. 46.5) [23]. CT accurately depicts the severity and extent of airway stenosis and helps differentiate intrinsic from extrinsic disease. CT also helps separate primary malignancy from metastases and distinguish tumor from atelectasis or post-obstructive pneumonia [2, 26]. Post-processed images, such as virtual bronchoscopy, can render the tracheobronchial tree in a visual format familiar to the clinician. This can assist in planning palliative interventions, such as stenting or ablative therapies, complementing conventional bronchoscopy to improve the technical success of airway recanalization (Fig. 46.6) [2]. FDG-PET will accurately discriminate a malignant hilar mass from adjacent post-obstructive atelectasis; however, patient preparation, imaging acquisition time, and availability limit its usefulness in the emergent setting [1].

Esophagorespiratory Fistula Esophagorespiratory fistula formation is a relatively rare but potentially devastating complication of esophageal and bronchogenic carcinoma, occurring in up to 22% of esophageal malignancy and around 1% of bronchogenic carcinoma [27, 28]. Nodal metastases and lymphoma can erode into the esophagus and airways and have also been implicated in esophagorespiratory fistula development [28, 29]. The risk of death is related to sepsis from repeated episodes of aspiration or from overwhelming lung infection [27]. Chest radiography findings are nonspecific and can include airspace consolidation, lung abscess, and pleural effusion resulting from aspiration of secretions and ingested material [29].

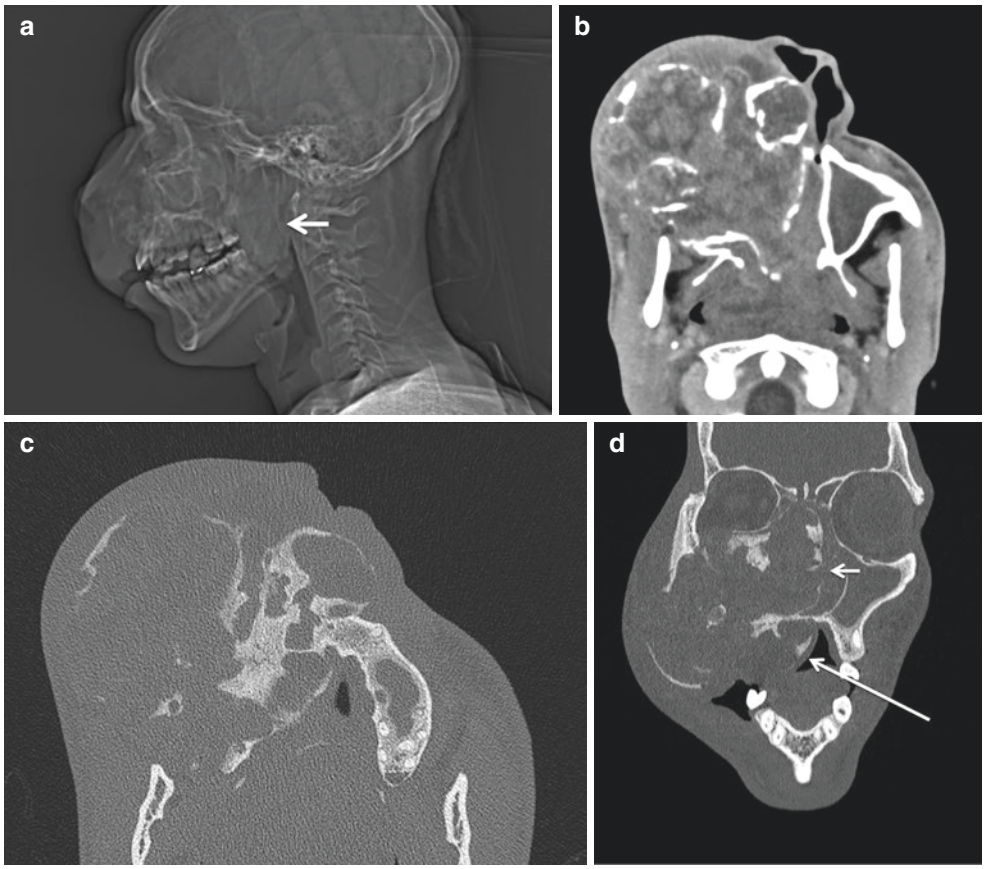

Fig. 46.5 Patient presenting to the emergency department with dyspnea. This case of advanced ameloblastoma of the right maxillary alveolar ridge in a young man demonstrates tumor mass effect involving the face and upper airway. The lateral scout image from head CT (**a**) depicts facial deformity as well as tumor replacing much of the nasopharynx (*white arrow*). Axial contrast-enhanced facial CT using soft tissue window (**b**) and bone window (**c**) depicts substantial mass effect in the right lower face and widespread local bone destruction. Coronal image (**d**) demonstrates the complete occlusion of the nasal cavity from tumor invasion and mass effect (*short arrow*) and substantial mass effect on the oral cavity (*long white arrow*)

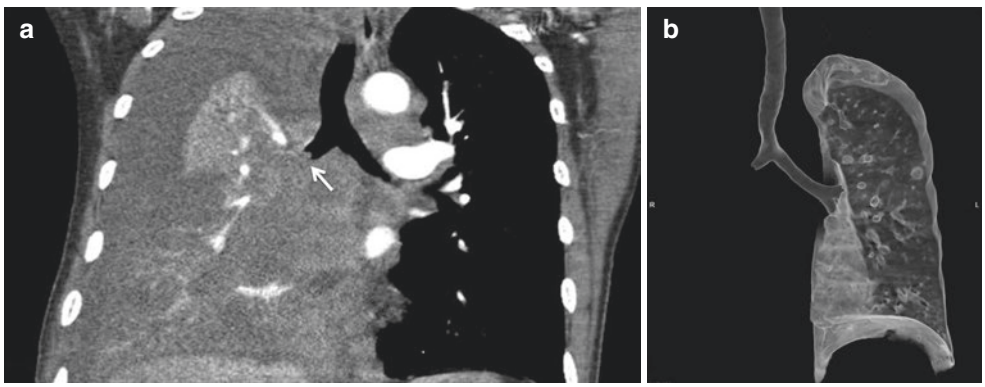

Fig. 46.6 Coronal contrast-enhanced chest CT (**a**) in a patient with squamous cell carcinoma demonstrates soft tissue occluding the right main bronchus *(arrow)* with total collapse of the right lung, inseparable from malignant tissue. Volume-rendered virtual bronchoscopy was created from the original contrast-enhanced chest CT dataset (**b**)

Fluoroscopic evaluation of the aerodigestive tract during the administration of an oral contrast agent will depict simultaneous opacification of the esophagus and tracheobronchial tree distal to the fistula. This procedure is best performed using a low-osmolar, water-soluble, iodinated contrast agent (iohexol), as large volumes of aspirated barium can compromise alveolar oxygen exchange and extravasated barium can incite an inflammatory response in the mediastinal soft tissues. Aspiration of high-osmolar, water-soluble contrast agents can lead to pulmonary edema and should likewise be avoided [30]. Chest CT performed after orally ingested contrast (CT esophagram) may demonstrate a direct communication between the respiratory tract and esophagus at the site of fistula formation with additional findings of ingested contrast agent within the respiratory tract distal to the fistula [29]. Abnormal soft tissue is often identified in the region of the fistula, indicating the site of malignancy [31]. CT is helpful in evaluating the extent and number of fistulas and the presence of a possible esophagorespiratory fistulous communication [29]. Virtual bronchoscopy or esophagography can enhance diagnostic confidence and serve as a component of treatment planning for emergent intervention [29].

Superior Vena Cava Syndrome Malignancy is responsible for 90% of cases of superior vena cava syndrome (SVCS) [32]. Benign causes of SVCS include thrombosis from

indwelling catheters, fibrosing mediastinitis due to immune response to *Histoplasma capsulatum* or tuberculosis, prior radiotherapy, cardiac pacer wires, and Behçet disease [27, 32, 33]. The clinical features of SVCS relate to venous congestion due to obstruction of the SVC from extrinsic compression by tumor or intraluminal occlusion from bland or tumor thrombus. Primary malignancy involving the superior vena cava resulting in SVCS is exceptionally rare [34]. Because bronchogenic carcinoma accounts for the majority of malignancy-related SVCS, chest radiography may reveal a lung mass with possible associated hilar or mediastinal involvement; however, cross-sectional imaging is necessary to confirm the diagnosis and identify the underlying etiology. Conventional venography was previously the imaging gold standard for diagnosing SVCS, but in contemporary practice, it is employed solely during endovascular intervention [34].

Contrast-enhanced chest CT is currently the preferred imaging modality for the assessment of SVCS. If this condition is suspected on the basis of clinical presentation, CT image acquisition following a 60-second delay optimally opacifies the systemic venous system and ideally characterizes the level (above or below the azygos arch) and extent of SVC obstruction [34]. Practically speaking, however, the diagnosis is often made on routine chest CT or CTPA protocol, which use shorter time delays [34]. Features of contrast-enhanced chest CT include complete occlusion of the SVC, an intraluminal filling defect within the SVC, marked narrowing of the SVC from surrounding soft tissue, and opacification of mediastinal or chest wall venous collateral vessels (Fig. 46.7) [34]. Included images of the upper abdomen may demonstrate intense enhancement of the medial segment of the left hepatic lobe ("quadrate lobe"), reflecting collateralization of the superficial epigastric veins and the left portal vein [34]. CT imaging findings of SVC obstruction may precede the development of the clinically apparent syndrome and present an opportunity for early intervention [32]. The underlying cause of the obstruction, most commonly bronchogenic carcinoma, lymphoma, or extrathoracic metastatic disease when considering malignant etiologies, will also be depicted at CT, representing a critical diagnostic advantage over catheter venography [31]. Although enhancement of soft tissue within the SVC represents intraluminal tumor, presumptive soft tissue enhancement without pre-contrast images for reference can be misleading. CT axial images and post-processed coronal and sagittal reformatted images also assist in planning for endovascular interventions. MRI approaches 100% sensitivity and specificity in the diagnosis of SVSC but is rarely used in the emergent setting due to limited scanner availability and patient factors [32].

Endovascular stenting has replaced chemotherapy and radiation therapy as the treatment of first resort in malignant SVCS, except in the case of chemotherapy-sensitive lymphoma, due to rapid clinical response and established long-term patency [32]. SVC stenting is carried out in the angiography suite. Under ultrasound guidance, the internal jugular, femoral, or subclavian vein is accessed, and superior vena cavography is performed to confirm the extent of disease and inform stent selection and placement. Using guidewires, the obstruction is traversed, and progressive dilatation of the obstructed lumen is optionally preformed prior to stent placement. In addition, local thrombolysis and mechanical thrombectomy may reduce the length of obstruction and risk of pulmonary emboli; however, thrombolysis has been associated with an increased risk of periprocedural bleeding [32]. A self-expanding endoprosthesis is deployed across the obstruction, taking care to not apply excessive pressure, which can result in SVC rupture and cardiac tamponade [32]. A chest radiograph is usually obtained following the procedure to confirm satisfactory stent placement and to serve as a baseline reference for future imaging. Reduction in symptoms is immediate, and clinical response to stenting is around 96% in bronchogenic carcinoma [35]. Recurrence

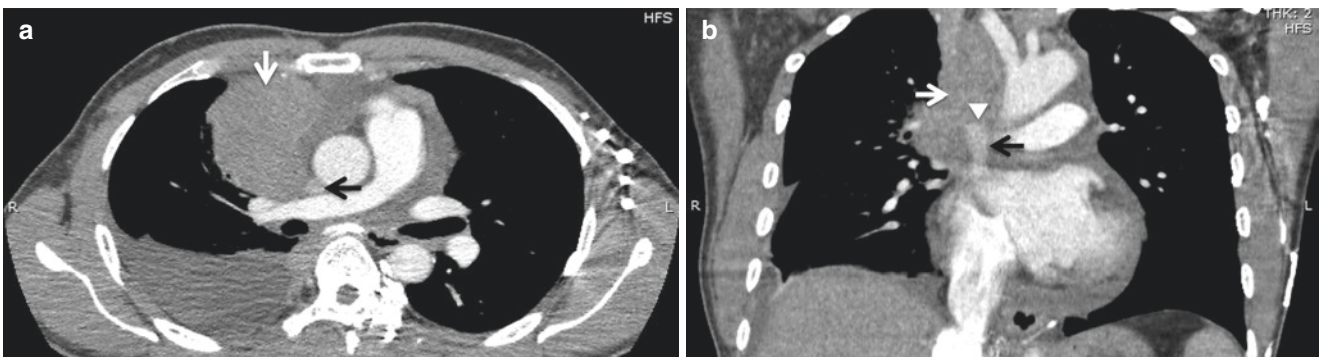

Fig. 46.7 Axial (**a**) and coronal (**b**) contrast-enhanced chest CT images demonstrate malignant SVC occlusion in this patient presenting with clinical SVC syndrome. Bulky enhancing soft tissue mass (*short arrows*) obliterates the expected location of the SVC. The inferior portion of the SVC is narrowed and displaced medially on the coronal image (**b**), superior to which SVC cutoff from tumor involvement is noted (*arrowhead*). Tissue sampling revealed bronchogenic carcinoma. A right pleural effusion is also present

of obstruction has been reported with an incidence of 0–40% [36]. Repeat stent placement is indicated in these cases and is associated with a high success rate [36].

Massive Hemoptysis Massive hemoptysis is generally defined as expectoration of ≥300–600 mL of blood within a 24-hour period and is associated with a 9–38% mortality rate [37, 38]. While pulmonary tuberculosis is the leading cause of hemoptysis worldwide, bronchogenic carcinoma is the most common malignant etiology [38]. Unstable patients presenting with massive hemoptysis are usually initially managed with bronchoscopy, which localizes the site of bleeding in the airways with a 73–93% diagnostic yield, and can be used for hemostasis [37]. Chest CTA performs equally well in determining the site of hemorrhage and is superior to bronchoscopy in identifying the underlying cause [37]. Chest radiography may reveal a lung mass, cavitary lesion, consolidation, or mediastinal mass, but up to 10% of patients with malignancy as the cause for hemoptysis may have a normal chest radiograph [39]. In most patients, chest CTA with post-processing is the diagnostic study of choice and can identify the site, underlying cause, and vascular origin of bleeding with a high degree of accuracy [38]. In 90% of patients with massive hemoptysis, a bronchial artery source is implicated [37]. On chest CTA, an abnormally dilated (≥2 mm diameter) or tortuous bronchial artery is suspicious for source of bleeding and targeted for embolization (Fig. 46.8) [38]. Active extravasation of contrast, while highly specific, is relatively rare and presents in only 3.6–10.9% of cases [38].

In addition to high diagnostic yield, chest CTA aids in planning the approach for catheter angiography and has been shown to decrease procedure time and technical success rate of subsequent embolotherapy [37, 38]. Bronchial artery embolization is an effective and safe treatment for massive hemoptysis with documented 73–99% success in effecting immediate control of bleeding [38]. Recurrence occurs in 10–29% in the first month and relates to incomplete embolization due to extensive disease or an occult non-bronchial source [38]. These patients are usually effectively retreated with embolization.

Pulmonary Embolism Acute pulmonary embolism (PE) is a leading diagnostic consideration in the oncologic patient presenting with acute chest pain. Left untreated, acute PE can be fatal [40]. Cancer patients are at particularly heightened risk for thromboembolic disease due to hypercoagulability. Used in conjunction with various clinical decision instruments to measure pretest probability, imaging plays an essential role in the diagnosis. As with any patient presenting with acute chest pain, chest radiography is used as an initial screening modality, although most patients with acute PE will have a normal chest radiograph [40]. The Westermark sign (geographic lucency related to regional oligemia from pulmonary arterial obstruction) and Hampton hump (wedge-shaped, peripheral consolidation representing infarcted lung tissue), though classically associated with acute PE, are rarely seen in practice. More commonly, atelectasis or airspace consolidation may be present in a minority of patients, but these findings are not specific [40]. The chief utility of chest radiography is to exclude other etiologies for chest pain, including pneumonia, pneumothorax, or pleural effusion [40]. In addition, chest radiography is helpful in interpreting ventilation-perfusion scintigraphy.

After excluding other causes of acute chest pain, CTPA is the imaging modality of first resort for diagnosis of acute PE. CTPA has well-established diagnostic accuracy, with 86% positive predictive value and 95% negative predictive value, having surpassed catheter pulmonary arteriography as the imaging gold standard [40, 41]. On CTPA, a centrally located hypodense intraluminal filling defect within the densely opacified pulmonary arterial system is seen in acute PE (Fig. 46.9) [40, 41]. Suboptimal vascular opacifi-

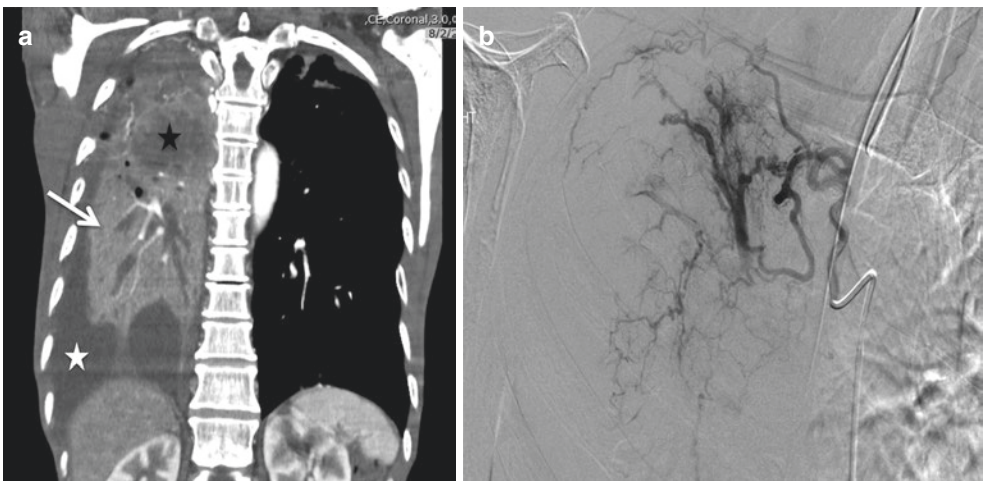

Fig. 46.8 (**a**) Coronal contrast-enhanced chest CT in a patient with massive hemoptysis depicts a hypodense right suprahilar mass (*black asterisk*) and subtotal right lung collapse (*arrow*). Pleural fluid is also seen adjacent to the collapsed lung (*white asterisk*). (**b**) Accompanying bronchial artery angiography with dilated and tortuous bronchial arteries, which were subsequently embolized, resulting in hemostasis

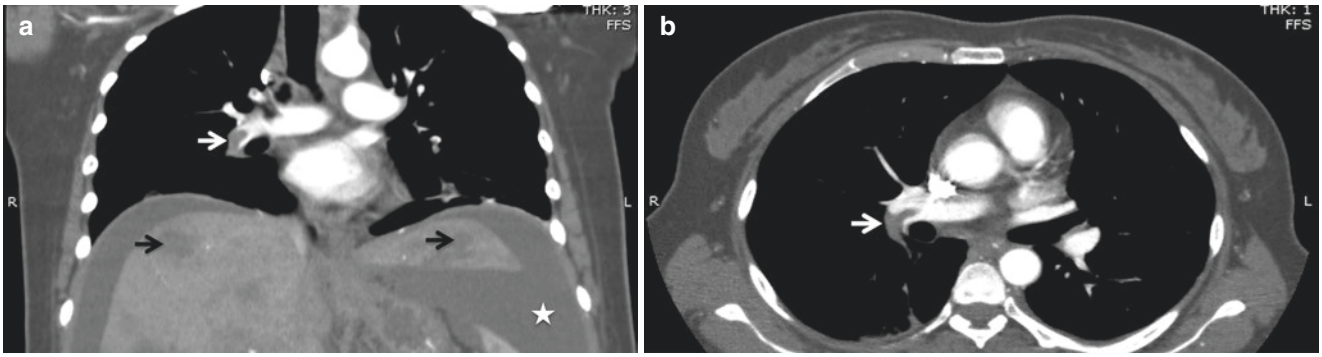

Fig. 46.9 Coronal (**a**) and axial (**b**) contrast-enhanced chest CT images demonstrate a hypodense filling defect in the contrast-opacified lumen of the right main pulmonary artery, with extension into the interlobar pulmonary artery, compatible with acute pulmonary embolism (*white arrows*). Also visible in the upper abdomen are multiple hepatic metastatic lesions (*black arrows*) and malignant ascites (*asterisk*)

cation and respiratory motion can reduce the diagnostic accuracy of CTPA, with a nondiagnostic rate of around 6%, whereas V/Q scintigraphy is inconclusive in over 25% of cases [40]. Incorporation of dual energy in CTPA has demonstrated improved sensitivity in detecting segmental and subsegmental pulmonary emboli [42]. Incidental but important additional findings can be detected with CTPA, such as pulmonary nodules and mediastinal lymphadenopathy [41].

Doppler and grayscale sonography of the deep venous system in the extremities is frequently employed as an adjunct to CTPA, since 36–45% of patients with acute PE have proximal deep venous thrombosis (DVT) [41]. Features of DVT on sonography include visualization of intraluminal thrombus, loss of venous compressibility, venous distention, and absence or diminution of Doppler color or spectral signal [40]. Serial negative extremity ultrasound examinations may obviate the need for additional investigative procedures or treatment in patients who are not candidates for CTPA related to renal insufficiency or adverse reaction to iodinated contrast or for whom CTPA or V/Q imaging is indeterminate [40]. By the same token, patients with evidence of extremity DVT by ultrasound and high pretest clinical suspicion for acute PE can be treated empirically without confirmatory imaging [41]. MR pulmonary angiography (MRPA) with and without gadolinium-based contrast agents has been studied in the evaluation of acute PE. Despite good documented diagnostic performance in technically adequate examinations, MRPA is currently not recommended for routine use due to limited availability and expertise in interpretation and suboptimal technical success [41].

Pericardial Effusion and Pericardial Tamponade Pericardial effusion and tamponade can be caused by primary malignancy in the chest, metastatic disease from a remote primary location, and following treatment for malignancy [43]. Common primary malignancies associated with pericardial effusion include bronchogenic carcinoma, breast carcinoma, lymphoma, and leukemia [43]. Lymphatic obstruction by tumor deposits is the predominant mechanism responsible for the development of malignant pericardial effusion, although direct contiguous extension (bronchogenic, esophageal, and breast) and hematogenous spread of tumor (lymphoma and leukemia) are other notable pathways for pericardial malignant disease [44]. Primary pericardial malignancies, such as mesothelioma or fibrosarcoma, are exceptionally rare etiologies for pericardial effusion [45, 46]. If accumulation of pericardial fluid is rapid, as little as 200–250 mL can result in tamponade physiology due to the relative inextensibility of the parietal pericardium [44].

A large pericardial effusion will result in an enlarged cardiac silhouette with a "water bottle" conformation on chest radiography [47]. On echocardiography, a pericardial effusion is readily apparent, and prolonged right atrial collapse during late diastole and right ventricular collapse in early diastole are characteristic for cardiac tamponade [47]. In the emergent setting, contrast-enhanced chest CT is ideally suited to establish the presence, extent, and possible cause of a pericardial effusion leading to tamponade. Fluid measuring near-water attenuation suggests a simple effusion, whereas higher-density fluid caused by hemorrhagic tumor deposits and cellular debris is often seen in malignant pericardial effusion [48]. An irregularly thickened (≥2 mm) pericardial lining with enhancing nodularity is highly suspicious for a malignant etiology in the appropriate setting, although mycobacterial infection can also have this appearance (Fig. 46.10) [48]. If a lung or chest wall mass and/or mediastinal adenopathy are present on CT, these findings would lend support to a malignant cause of a pericardial effusion. Definitive diagnosis is made by cytological examination of aspirated fluid. Treatment by pericardiocentesis with or without drain placement is performed with CT or echocardiography guidance [25, 31].

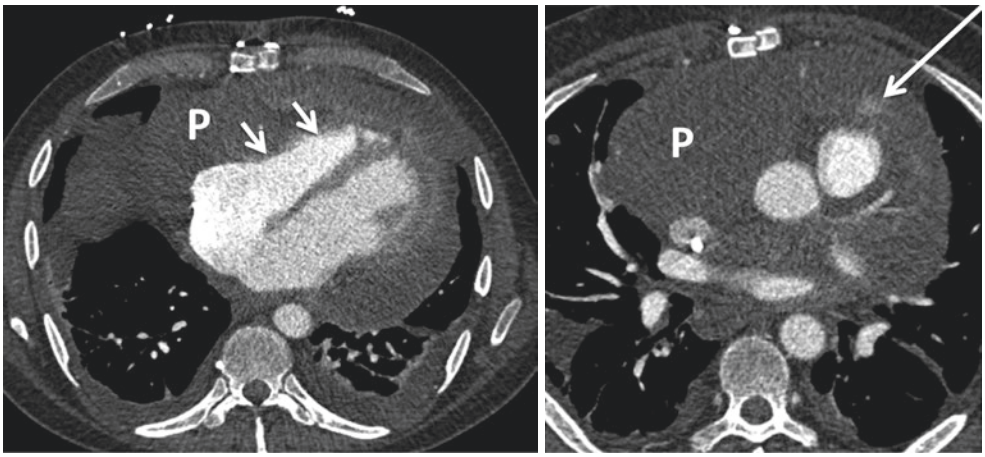

Fig. 46.10 Contrast-enhanced axial chest CT in a patient with metastatic melanoma depicts a large pericardial effusion (P). Findings are compatible with malignant effusion by CT given the effusion density and the nodular enhancing tumor foci (*long arrow*). Flattening of the right ventricular wall is suggestive of cardiac tamponade physiology (*short arrows*)

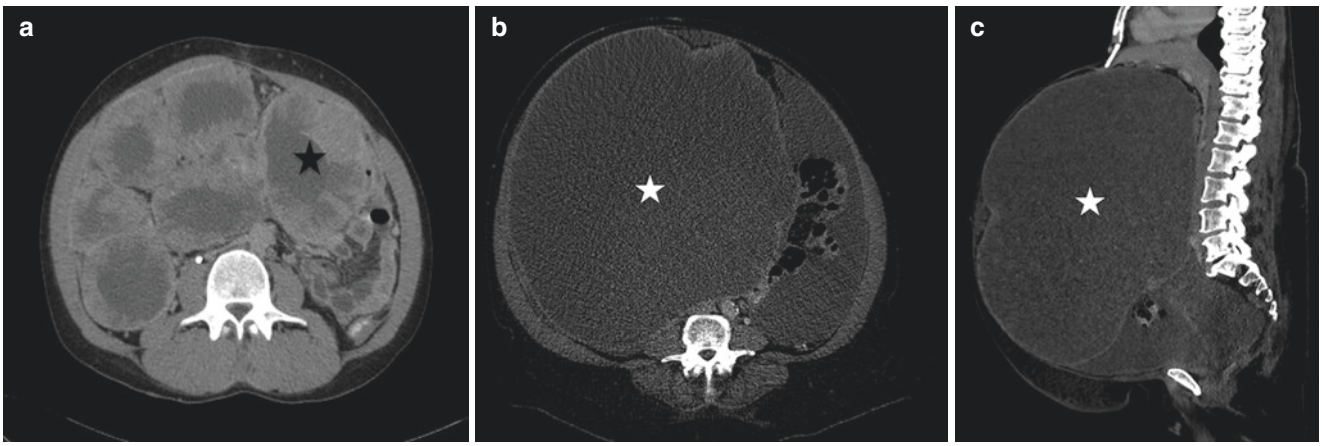

Fig. 46.11 Certain tumors, particularly late in a patient's disease course, can exert substantial mass effect in the peritoneal cavity. By virtue of this mass effect, they can compress the GI or GU tracts and result in early satiety, nausea, vomiting, and bowel or ureteral obstruction, respectively. A contrast-enhanced axial CT image of the abdomen and pelvis (**a**) demonstrates multiple large peripherally enhancing peritoneal implants from choriocarcinoma (representative lesion indicated by a black asterisk), which significantly displace normal structures. In a different patient, axial (**b**) and sagittal (**c**) contrast-enhanced CT images of the abdomen and pelvis demonstrate bulky multicystic masses (*white asterisks*) with very thin walls arising from a mucinous ovarian cystadenoma

Abdominopelvic Emergencies

Bowel Emergencies Bowel obstruction in patients with abdominal or pelvic malignancy results from impingent on the bowel lumen, either from intrinsic mural disease or from extramural compression usually from serosal implants (Fig. 46.11). In addition, many oncologic patients have undergone prior abdominal or pelvic surgery, which predisposes to bowel obstruction secondary to adhesions [49]. Bowel obstruction may also result from complication of treatment. For example, nivolumab, which is an immunotherapeutic agent for lung cancer, has been associated with increased risk of small bowel obstruction and perforation [50]. Colorectal carcinoma (10–30%) and ovarian malignancy (20–50%) are the most common cancers associated with bowel obstruction. Metastatic disease is more commonly implicated than primary malignancy in small bowel obstruction, as it is usually secondary to compressive effects from peritoneal metastases; however, primary gastrointestinal malignancy can rarely result in obstruction (Fig. 46.12). Additional primary cancers that can present with peritoneal metastases, and predispose to small bowel obstruction, include gastric, pancreatic, breast, and lung [49].

In the emergent setting, suspected bowel obstruction is often initially assessed with abdominal radiography. Supine abdominal radiographs may demonstrate abnormally dilated small bowel (≥2.5 cm in diameter) in small bowel obstruction and small bowel and colon in colonic obstruction [51]. Upright abdominal radiographs may show multiple air-fluid levels or, in the case of viscus perforation, free air accumulation under the diaphragms. Plain radiography is only around 50–60% accurate in the evaluation of small bowel obstruction and does not adequately predict the site of obstruction [51, 52]. Contrast-enhanced CT of the abdomen and pelvis is the imaging of choice when evaluating for bowel obstruc-

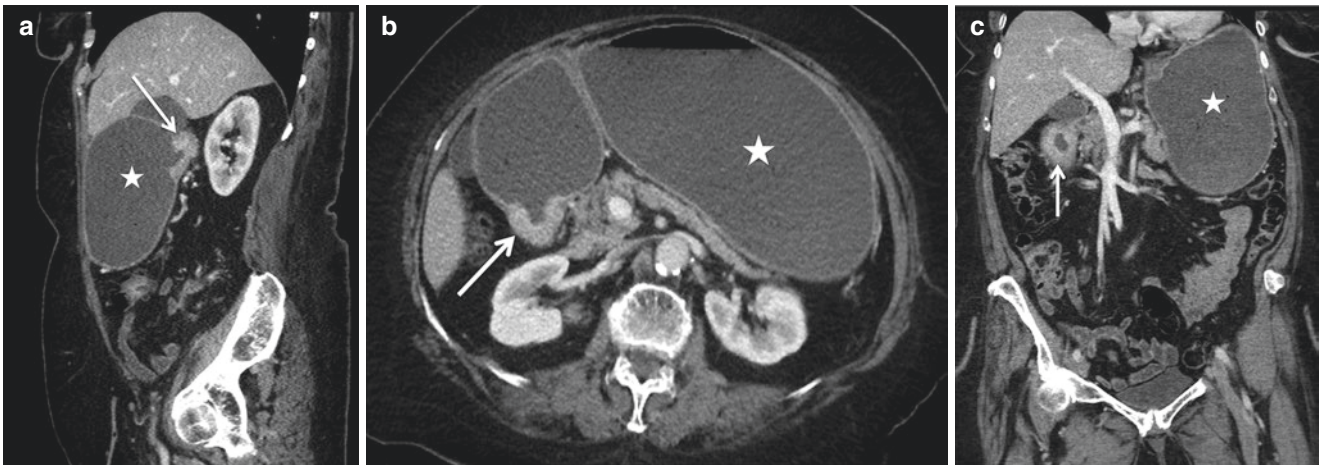

Fig. 46.12 A 57-year-old presented to the emergency department with nausea and vomiting. Sagittal (**a**), axial (**b**), and coronal (**c**) contrast-enhanced CT images of the abdomen and pelvis demonstrate a dilated fluid-filled stomach (*asterisk*). At the gastric antrum, there is irregular, enhancing wall thickening resulting in gastric outlet obstruction (*arrows*). Pathology revealed poorly differentiated gastric adenocarcinoma of the distal stomach and pylorus

tion, with far superior accuracy in securing the diagnosis (95%) and locating the site of obstruction [52]. On CT, dilated small bowel ≥2.5 cm (outer wall-to-outer wall) is seen proximal to a discrete transition point, distal to which the remainder of the small bowel and the colon are relatively decompressed (Fig. 46.13) [51]. Abnormal enhancing or necrotic soft tissue may be seen in the region of the transition point, representing peritoneal metastatic disease or, rarely, primary bowel malignancy. In contradistinction to small bowel obstruction, large bowel obstruction is most often caused by primary colorectal malignancy as opposed to metastatic disease [53]. Large bowel obstruction is diagnosed when both small bowel and colon (≥9 cm for cecum, otherwise ≥6 cm) are dilated proximal to a transition point within the colon [54]. Differentiating a transition point from a post-inflammatory or ischemic stricture in large bowel obstruction on CT can be difficult given similar imaging appearances. The presence of enlarged local lymph nodes may suggest a malignant etiology. Oral or rectal contrast is typically not administered except for suspected bowel complications, such as perforation or fistula or sinus tract formation [52, 55]. MRI is generally not used for evaluating bowel obstruction and is often reserved for pregnant or pediatric patients, in whom ionization radiation exposure is of particular concern.

Among patients with spontaneous pneumoperitoneum secondary to bowel perforation, 14% are attributable to malignancy [56]. Plain radiography is diagnostic in only 30–59% of cases of free intraperitoneal gas but approaches 100% accuracy in large-volume pneumoperitoneum [56]. Radiographic signs include free air under the diaphragms, increased bowel wall visualization from the presence of extraluminal and intraluminal gas (Rigler sign), lucency outlining the falciform ligament (falciform ligament sign), and air outlining the entire abdominal cavity (football sign) and a hyperlucent liver [56]. Abdominal radiography cannot pre-

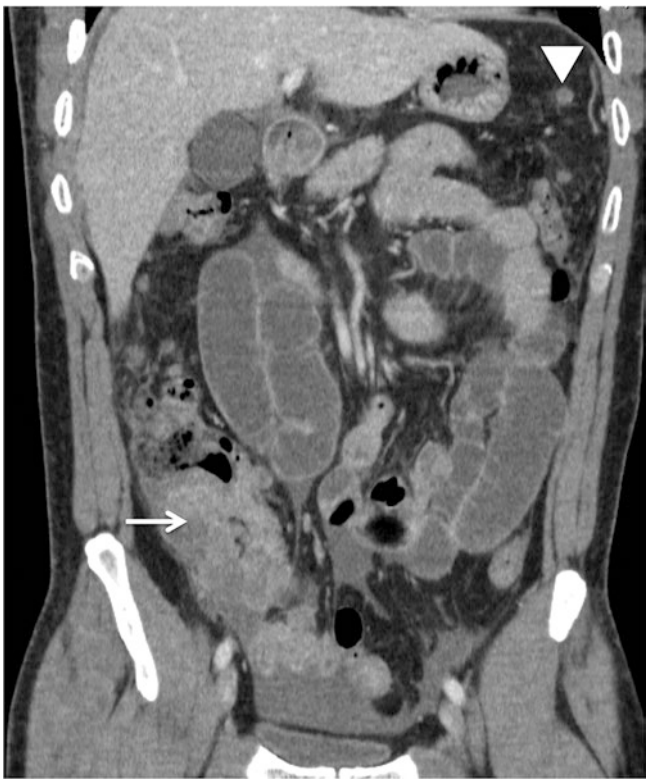

Fig. 46.13 Single coronal contrast-enhanced CT image of the abdomen and pelvis in a patient presenting with nausea and vomiting demonstrates a heterogeneously enhancing cecal-region mass (*arrow*). There are dilated, fluid-filled segments of small bowel, compatible with small bowel obstruction. Pathology revealed appendiceal carcinoma. Note serosal metastatic implants (*arrowhead*)

dict the site of perforation. CT, however, is exceedingly sensitive for the detection of free intraperitoneal gas (96–100%) and can correctly identify the site of perforation with 80–90% accuracy [56]. CT features of bowel perforation include discrete bowel wall defect and extraluminal gas, oral or rectal contrast, or bowel contents [56]. Both colorectal carcinoma and gastrointestinal lymphoma are complicated by perforation with a prevalence of up to 9%, and systemic chemotherapy has been observed to further increase the risk of perforation in bowel lymphoma [57].

Ischemic colitis can coexist with colonic malignancy with an incidence of up to 7%, and 20% of patients with ischemic colitis have an underlying colorectal cancer [58, 59]. Ischemic colitis secondary to malignancy can result from increased intraluminal pressure and subsequent diminished blood flow in the dilated colon proximal to site of primary malignancy. In cases without mechanical obstruction, bacterial overgrowth in stagnant segments of colon has been implicated in ischemic colitis [60]. Pancreatic adenocarcinoma can compress the superior mesenteric artery and vein, resulting in critically diminished perfusion and subsequent bowel ischemia [60]. Metastases to the mesenteric root, including colon, breast, ovarian, and lung primaries, can similarly result in bowel obstruction by direct vascular impingement [1]. In ischemic bowel, contrast-enhanced CT of the abdomen and pelvis is the imaging modality of choice, and features include mural thickening, submucosal edema (low attenuation) or hemorrhage (high attenuation), engorgement of mesenteric vessels, mesenteric edema, altered or absent mucosal enhancement, and intramural gas or portal venous gas. Hypoenhancement of the bowel wall is considered the most specific sign for ischemic bowel, although these findings are often subtle. Dual-energy CT can increase the conspicuity of bowel wall hypoenhancement through the use of iodine maps or overlay images [61]. Permeation of intraluminal gas across damaged mucosa causes intramural gas and appears as focal or circumferential locules of air within the colonic wall (pneumatosis coli). Gas can then propagate into the mesenteric and portal veins, giving the appearance of air-attenuation filling defects within these vessels.

Intussusception is characterized by telescoping of a segment of bowel along with its corresponding mesentery into an adjacent segment of bowel. Whereas 95% of cases of intussusception are idiopathic in children, 80–90% of adult cases are associated with underlying mass lesions, referred to as "lead points," and are most commonly polypoid bowel neoplasms [62, 63]. In 30% of small bowel and 60% of colonic intussusceptions, an intramural or extrinsic lead point will be malignant [62]. With CT, intussusception is characterized by a "bowel-within-bowel" appearance with direct visualization of an inner bowel segment and surrounding fat (intussusceptum) enveloped by an adjacent outer segment of bowel (intussuscipiens), with or without accompanying vessels, rendering a targetoid or sausage-like appearance [53, 63]. Intussusception can be complicated by bowel obstruction or ischemia, the features of which are described above.

Spontaneous Intra-abdominal Hemorrhage Spontaneous hemorrhage from visceral organ malignancy is a rare, but potentially catastrophic, oncologic emergency. Around 10–15% of patients with hepatocellular carcinoma will present to the emergency department with tumor rupture leading to intraparenchymal hematoma, subcapsular hematoma, hemoperitoneum, or some combination. Risk factors for spontaneous hemorrhage of hepatocellular carcinoma include peripheral or subcapsular location and large tumor size [64]. Hypervascular metastases to the liver, such as melanoma and renal cell carcinoma, are at particularly heightened risk for spontaneous hemorrhage. Reports of spontaneous hemorrhage from primary angiosarcoma of the liver have been documented [3]. Although spontaneous splenic rupture is more commonly reported in infection, notably cytomegalovirus, Epstein-Barr virus, or malaria, lymphomatous or leukemic splenic involvement can also give rise to severe hemorrhage, necessitating immediate endovascular treatment or splenectomy [65].

Spontaneous tumor rupture is evaluated with contrast-enhanced CT of the abdomen and pelvis in order to confirm the presence of rupture, identify the site of involvement, and determine the extent of hemorrhage (Fig. 46.14). The appearance of extravascular blood on CT varies in a time-dependent manner. Acute blood products will demonstrate an attenuation in the range of 30–45 HU, whereas clotted blood has attenuation values from 45 to 70 HU [3]. When a focal area of high-density clotted blood is seen in the abdomen or pelvis on a background of lower-density unclotted blood, it is referred to as the "sentinel clot" and points to the site of primary source of bleeding [3, 53]. On occasion, ongoing bleeding can be seen during the acquisition of CT images as active extravasation of contrast, with focal areas of high-density (85–370 HU) extraluminal IV contrast material and surrounding clotted hematoma [66]. Ongoing bleeding requires emergent surgical or endovascular interventions to control blood loss. In this setting, particularly with unstable patients, catheter angiography and catheter-directed embolization can aid in management.

Urinary Obstruction Approximately one-quarter of patients with pelvic or retroperitoneal malignancy will develop life-threatening urinary obstruction [1]. Progressive urinary tract obstruction most often results from compression or invasion of the ureters, most commonly the distal one-third of the ureters below the level of the common iliac

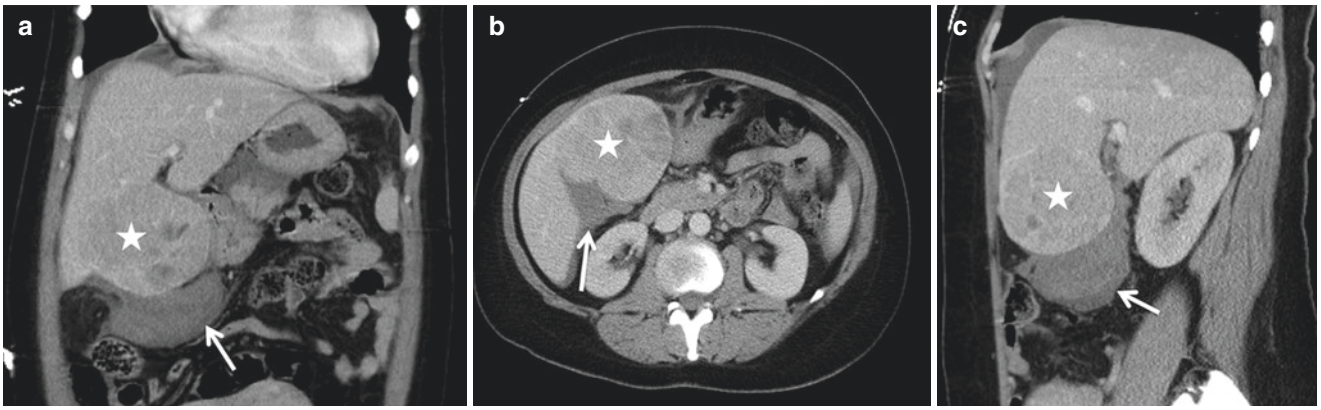

Fig. 46.14 A 47-year-old patient presented to the emergency department with acute-onset right upper quadrant pain. Coronal (**a**), axial (**b**), and sagittal (**c**) contrast-enhanced CT images of the abdomen reveal a heterogeneously enhancing exophytic hepatic mass (*asterisk*) arising from the right hepatic lobe. There is surrounding high-density fluid, compatible with blood products (*arrows*). Pathology revealed hemorrhagic hepatocellular carcinoma

arteries, by primary malignancies such as prostate, bladder, cervical, ovarian, or colorectal [1, 67]. Lymphoma and sarcoma, and less likely retroperitoneal metastatic disease from primary cancers such as cervix, urinary bladder, prostate, colorectal, ovary, and testes, can likewise result in ureteric obstruction by direct tumor invasion or compression [1, 67].

Hydronephrosis and hydroureter can be identified by ultrasound as expansion of the renal collecting systems and ureters with anechoic urine. The obstructing mass may not be evident on ultrasound, and advanced cross-sectional imaging is usually required to assess for the presence, size, and location of the malignancy. In the emergent setting, CT is often initially employed either as a standard single-phase postcontrast CT or formal CT urography. In single-phase CT, both the obstructed urinary tract and offending lesion are clearly depicted. A delayed enhancement pattern of the ipsilateral kidney may be present, reflecting compromised excretion of contrast due to downstream obstruction (Fig. 46.15). CT urography is not often employed in the acute setting but would consist of an unenhanced image set, followed by nephrogenic phase (100 seconds after IV contrast administration) and excretory phase (3 minutes after IV contrast administration) imaging [68]. The urographic component, however, may be limited in severe obstruction, which would inhibit excretion of contrast. Treatment of malignant urinary obstruction is palliative, as median survival is measured in months [67, 69]. Nephroureteral stent and percutaneous nephrostomy tube placement are the most common interventions for palliative urinary diversion [67].

Biliary Obstruction Obstruction of the biliary system from primary tumor invasion or compression of the bile ducts by hilar nodal metastases can result in significant morbidity and mortality [70]. Pancreatic adenocarcinoma, periampullary malignancy, and cholangiocarcinoma are most the most commonly implicated primary malignancies associated with biliary obstruction [70, 71]. In patients with known or suspecting malignancy presenting with jaundice, abdominal pain, and/or laboratory evidence of biliary obstruction, the obstructing mass and associated obstruction can be confirmed by abdominal ultrasound, CT, or MRI. CT and MRI offer the additional advantage of preprocedural planning and staging [72]. MR cholangiopancreatography (MRCP), which is always acquired in combination with conventional MRI of the abdomen, is a noninvasive imaging technique that provides exquisite anatomic detail of the dilated biliary tree and can often exclude choledocholithiasis as a cause of obstruction [73]. Endoscopic ultrasound can be complementary to CT and MRI/MRCP in difficult cases [72]. Pancreatic adenocarcinoma is typically characterized as an ill-defined and infiltrative mass, which is hypoattenuating with respect to normal pancreatic parenchyma on CT. In rare cases, pancreatic adenocarcinoma is indistinguishable from normal pancreatic tissue. When this occurs, the presence of malignancy in the pancreatic head can be inferred by the "double duct" sign, representing simultaneous common biliary and main pancreatic ductal dilatation [70]. Cholangiocarcinoma is classified as intrahepatic, hilar, or extrahepatic, and most occur at the bifurcation of the hepatic ducts (Klatskin tumor) [70]. At the time of presentation, the common imaging appearance of cholangiocarcinoma is biliary ductal dilatation, which can be focal or diffuse. On cross-sectional imaging, infiltrative hilar cholangiocarcinoma is further characterized by an ill-defined soft tissue mass with associated by bile wall thickening or complete duct luminal obliteration (Fig. 46.16). Intrahepatic (mass-forming) cholangiocarcinoma is hypovascular and demonstrates gradual centripetal enhancement in a time-dependent manner following IV contrast administration [70].

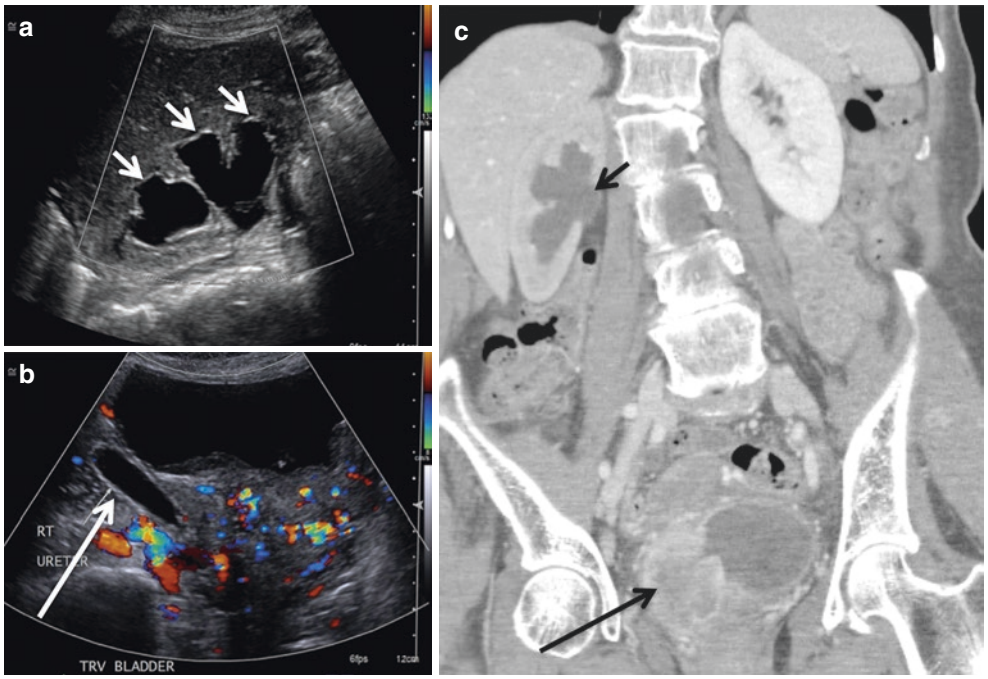

Fig. 46.15 A 70-year-old female with urinary bladder urothelial carcinoma. (**a**) Initial sonographic image shows dilation of the renal collecting system with calyceal blunting (*short white arrows).* Subsequent sonographic image of the pelvis (**b**) shows dilation of the distal ureter (long white arrow), with vascularized soft tissue mass in the urinary bladder. Coronal CT image (**c**) redemonstrates hydronephrosis (*short black arrow*) and confirms the enhancing mass in the right lateral aspect of the urinary bladder (*long black arrow*). Also present is relative hypoenhancement of the right kidney compared to the left kidney, termed a "delayed nephrogram," a finding often seen with higher-grade ureteral obstruction

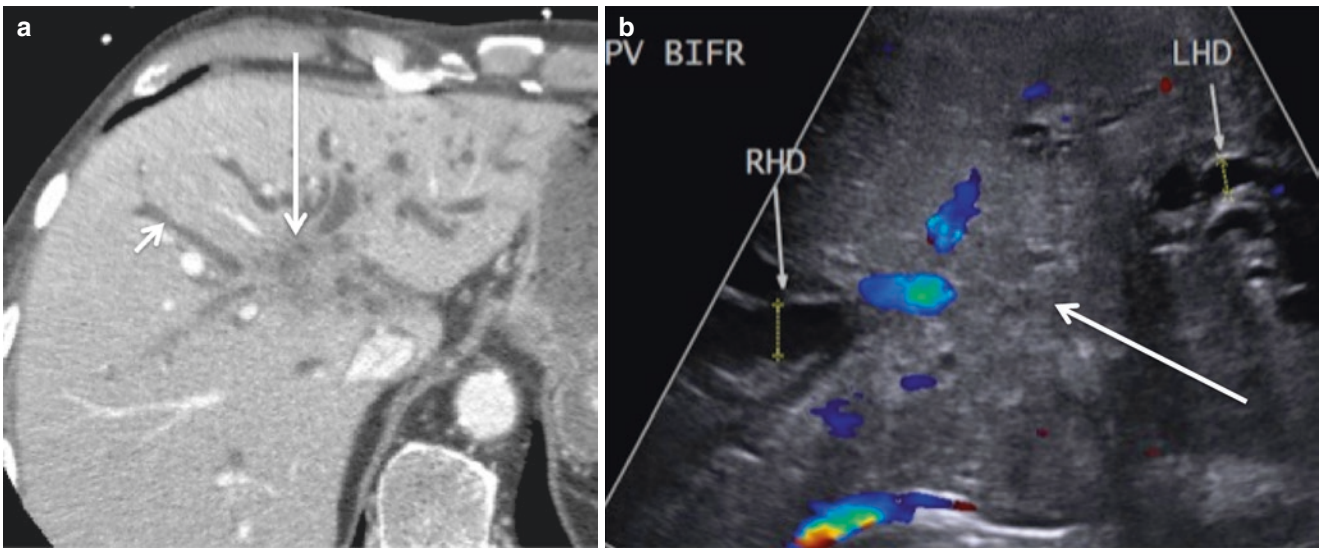

Fig. 46.16 Contrast-enhanced axial CT image of the abdomen (**a**) and transverse sonographic image centered at the hepatic hilum in a patient presenting to the ED with jaundice and right upper quadrant pain. The CT image depicts intrahepatic biliary ductal dilation (short arrow) and a hypoenhancing hepatic hilar mass, typical of cholangiocarcinoma (Klatskin tumor). Sonographic image of the right upper abdominal quadrant (**b**) demonstrates biliary ductal dilation and an ill-defined heterogeneous mass with Doppler signal, indicating vascularity. RHD, right hepatic duct; LHD, left hepatic duct

In patients with advanced malignant biliary obstruction, palliative biliary diversion can be performed surgically, endoscopically, or via a percutaneous approach. A surgical approach results in significant reduction in recurrent obstruction but is associated with a higher complication rate [71]. Endoscopic and percutaneous stenting using both plastic and metallic stents is associated with lower complication rates but higher reocclusion rates and need for repeat procedures [71, 74]. In general practice, bypassing distal biliary obstruction is usually initially attempted with ERCP, and percutaneous biliary drainage and stenting are reserved for endoscopic technical failure [74]. For proximal obstruction, both approaches can be taken, sometimes in combination; however, a percutaneous approach, which is usually carried out in the interventional radiology suite, may be more appropriate when drainage of segmentally dilated bile ducts is desired. This is because percutaneous ultrasound can first identify these structures, allowing for a more targeted subsequent intervention using fluoroscopic guidance [74].

Musculoskeletal Emergencies

Pathologic Fractures The musculoskeletal system is comprised of the axial and appendicular skeleton as well as the supporting muscles and soft tissues. Oncologic emergencies can affect both structural components, but skeletal complications are much more frequently encountered. Bone is the most common site for metastatic disease [75]. At postmortem examination, the incidence of metastatic bone disease was 73% in breast cancer, followed in frequency by prostate (68%), thyroid (42%), lung (36%), and renal (35%) [75]. The burden of osseous metastatic disease correlates to the frequency of skeletal-related events (SREs), which include fractures, surgical or therapeutic intervention for bone lesions, spinal cord compression, and hypercalcemia of malignancy [76].

The destruction of trabecular and cortical bone by primary or metastatic tumor degrades the intrinsic structural stability, and therefore the weight-bearing capabilities of bone, predisposing patients to pathologic fractures. These fractures occur in both the axial and appendicular skeleton but are more debilitating in the vertebra, pelvis, or lower extremities (Fig. 46.17).

Appendicular Skeleton Regarding the long bones, plain radiographs provide rapid initial screening. When fractured, subsequent orthopedic consultation and stabilization of a pathologic fracture restores functionality and decreases pain. If plain radiographs are not revealing, but there remains a high clinical concern for fracture, further imaging may be warranted. Specifically, in patients with low bone mineral density, nondisplaced fractures can be occult by plain radiography, and if the patient cannot bear weight or has unexplained pain, further evaluation with cross-sectional imaging may be warranted. Unenhanced MRI provides very sensitive evaluation for both metastatic involvement of bone and acute fracture; however, after-hours availability is not widespread. Normal bone marrow varies by location within bone and

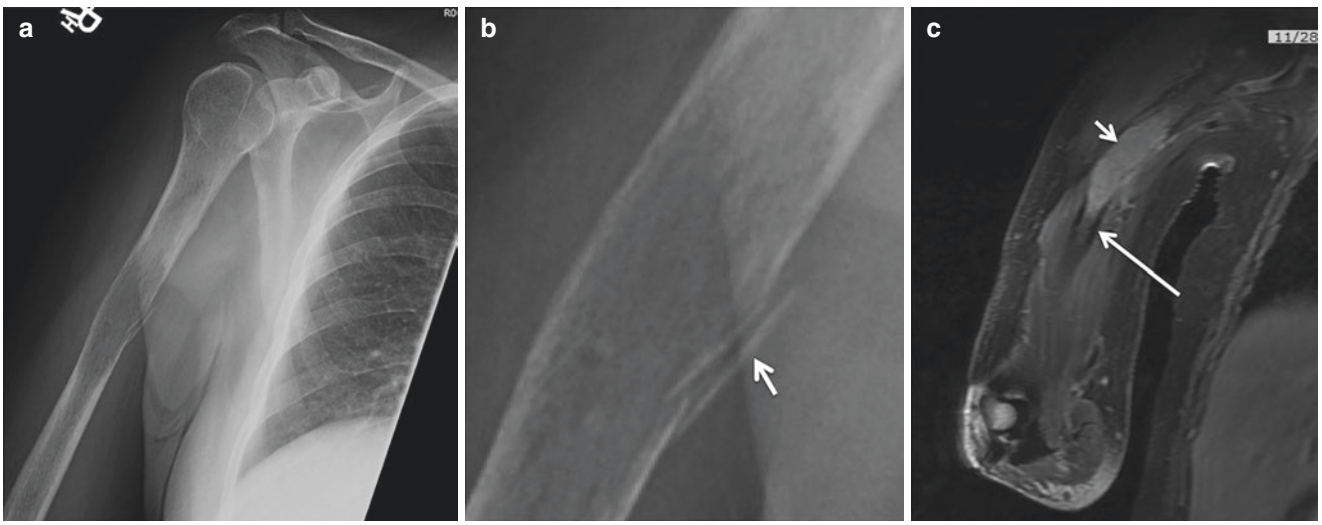

Fig. 46.17 AP radiograph of the humerus demonstrates a geographic, moth-eaten, lytic, destructive lesion, with cortical endosteal thinning and mild marrow cavity expansion (**a**). (**b**) Magnified image of the associated pathologic fracture with adjacent cortical fragments (*arrows*). Coronal T1 postcontrast fat-saturated MR image (**c**) demonstrates enhancing soft tissue mass replacing the normal fatty marrow cavity (*short arrow*) and obliterating the T1-hypointense cortex (normal cortex shown with *long arrow*). Diagnosis is plasmacytoma with pathologic fracture

patient age; however, in general normal marrow can be categorized as hematopoietic or fatty. Fatty marrow is T1-hyperintense and T2-hyperintense, while hematopoietic marrow is slightly hypointense on both sequences. The proportion of hematopoietic marrow decreases with patient age. Marrow can be replaced or infiltrated by metastases, leukemia, or lymphoma, resulting in T1 signal that is hypointense relative to skeletal muscle (which serves as an internal frame of reference) [77]. On fat-saturated T2 and STIR imaging, malignancy is usually hyperintense, resulting from intrinsically higher water content and reactive edema [77]. In the case of fracture, fluid-sensitive MRI sequences (T2 and T2 or PD with fat saturation) will demonstrate robust marrow edema, while T1 sequences are used to localize the site of cortical disruption. Unenhanced CT can be used in the emergent setting to identify and characterize fractures. The primary limitations of unenhanced CT in the evaluation of malignant involvement include diminished sensitivity for malignant soft tissue and early marrow metastatic disease.

Vertebral Fractures Metastatic disease to the spine is the most common form of skeletal malignancy, and osteolytic bone destruction may occur in up to two-thirds of patients [75]. As previously noted, plain radiography is widely available and rapid but relatively insensitive for pathologic vertebral body fractures. In the setting of trauma in cancer patients, if there is clinical concern for fracture, unenhanced CT is the imaging modality of choice for identification and characterization of fractures. With MRI, the presence of bone marrow edema (T2 or STIR hyperintensity) indicates an acute time course. The addition of IV contrast to an MR examination provides a more sensitive evaluation of epidural tumor extension but will not further characterize the underlying osseous malignancy and is not necessary in diagnosing fracture. This is because bone metastases do not always enhance after the administration of gadolinium. Sclerotic metastatic disease and treated or partially treated tumor foci, for example, typically do not enhance but will still be detected on MRI without IV contrast [77]. CT-guided vertebroplasty can help reduce pain in a wide variety of osteolytic vertebral lesions [78].

In the setting of vertebral fracture, spinal cord compression can result from retropulsion of bone fragments or soft tissue tumor into the spinal canal. Additionally, local hemorrhage resulting from the fracture can cause local mass effect and exacerbate spinal canal narrowing. MRI provides the optimal assessment of the spinal cord, including the degree and cause of narrowing and the presence or absence of spinal cord edema. For further information on this topic, please see the dedicated chapter on spinal cord compression. Image-guided treatment of this entity is discussed in the section on neuroradiologic emergencies.

Impending Fractures The Mirels classification system provides an overview of the risk of impending fracture in long bones, with a score ≥ 8 suggesting prophylactic surgical fixation [79–81]. The calculation of the Mirels score incorporates lesion site, nature of the osseous lesion, lesion size relative to cortical thickness, and pain, as follows:

- Location: upper limb (1 point), lower limb (2 points), and trochanteric region in the proximal femur (3 points).
- Lesion: blastic (1 point), mixed (2 points), and lytic (3 points).
- Size: the size of lesion expressed as a proportion of cortical involvement – less than 1/3 (1 point), 1/3 to 2/3 (2 points), and greater than 2/3 (3 points) [79, 81].
- Pain: subjectively classified as mild (1 point), moderate (2 points), or functional (3 points).

Imaging, usually consisting of both CT and plain radiography, is necessary in computing a Mirels score and can guide patient management by suggesting fixation prior to fracture.

Case Study

Introduction: A 67-year-old woman with 40-pack-year smoking history presents with a 1-month history of worsening lower back pain. She also reports that she has had 60-pound weight loss since the preceding year due to poor appetite and low energy from coughing all night. Physical exam is positive for diminished breath sounds over the right chest and tenderness to palpation over the mid-lower back. She undergoes chest radiography and CT of the abdomen and pelvis (Fig. 46.18)*. She returns to the emergency department 1 year later with acutely worsening low back pain and bilateral lower extremity hyperreflexia* (Figs. 46.19 and 46.20)**.**

Discussion: Findings are compatible with pathologic thoracic vertebral fracture secondary to metastatic disease from lung cancer. The spine is the most common location for skeletal metastasis and occurs in up to 10% of newly diagnosed cancers. Metastasis to the spine occurs due to hematogenous dissemination of malignant cells. On radiography and CT, metastases are classified as osteoblastic, mixed or osteolytic. Common primary malignancies that metastasize to the spine are lung (osteolytic), breast (mixed), and prostate (osteoblastic). In this case, the patient presented with osteolytic metastasis from metastatic lung cancer. In addition to metastasis, the differential diagnosis for lytic lesions in the spine includes primary bone tumors, multiple myeloma, lymphoma, discitis/osteomyelitis, and metabolic disorders.

Patients with metastatic disease to the spine present with spinal tenderness and, in more advanced cases, neurologic deficits. This may or may not be seen in setting of pathologic

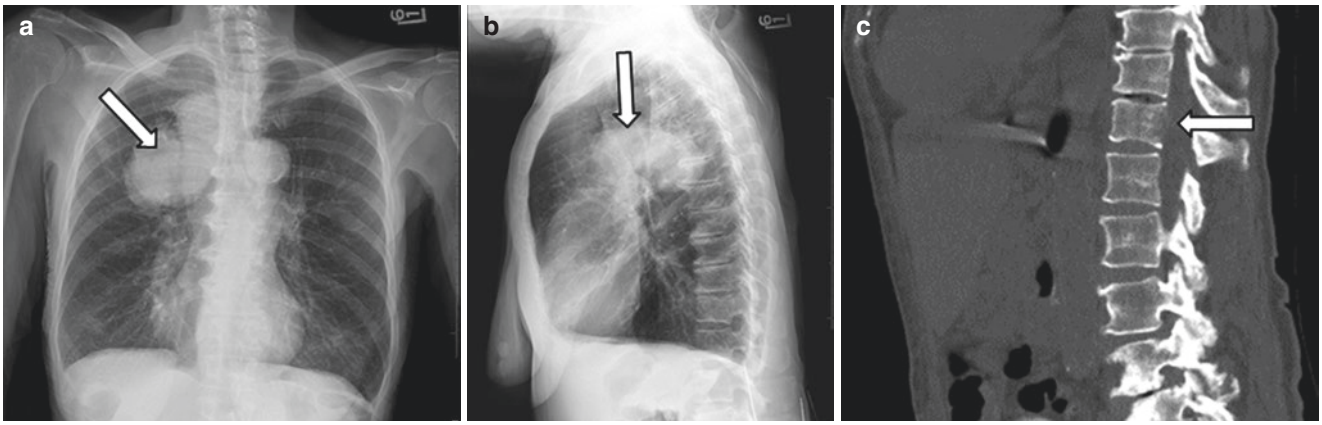

Fig. 46.18 *Case Study.* Imaging at initial patient encounter. Frontal (**a**) and lateral (**b**) chest radiographs demonstrate a lobulated right hilar/right upper lobe mass (*arrows* in images **a** and **b**) highly suggestive of malignancy. (**c**) Sagittal CT image of the abdomen demonstrates subtle erosion of the posterior vertebral body cortex of T12 (*arrow*)

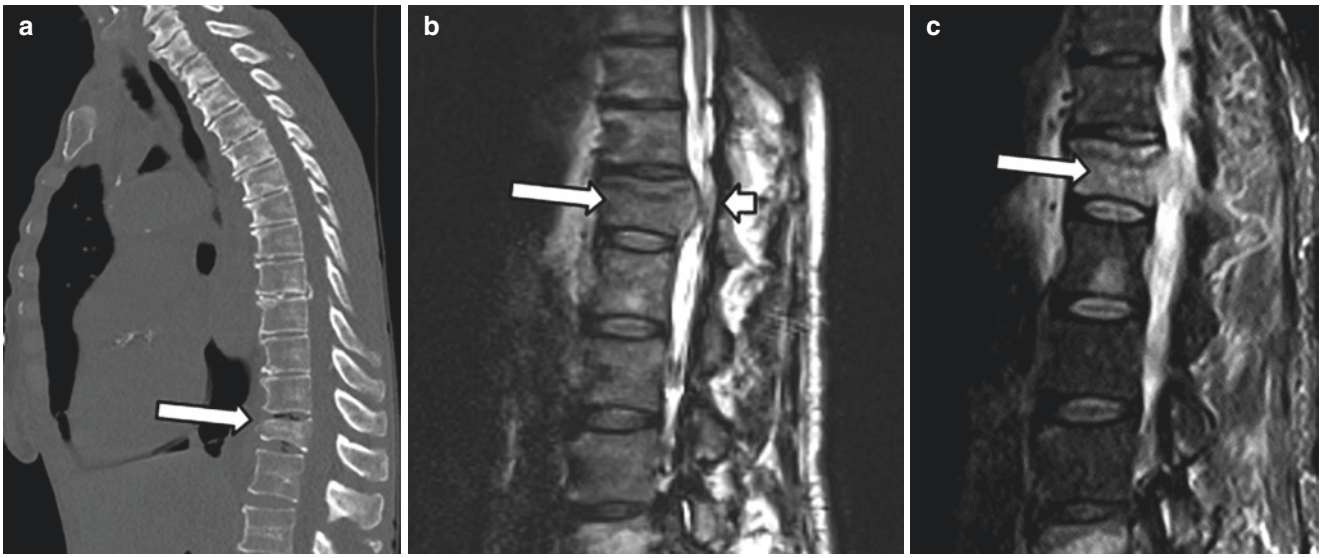

Fig. 46.19 *Case Study.* Imaging at follow-up patient encounter, 1 year later. Sagittal CT of the chest (**a**) demonstrates a wedging compression fracture of the T12 vertebral body with 50% anterior height loss (*arrow*); however, the age of this fracture is not definitively established by CT. T2-weighted MRI with fat saturation (**b**) demonstrates an acute pathologic compression fracture of T12 with bright marrow signal confirming the acute time course of this fracture

fracture and spinal cord compression. A Mirels score can be used to assess the risk of pathologic fracture, with a score greater or equal to 9 suggesting prophylactic fixation be performed. Treatment of pathologic fracture is multidisciplinary and involves a combination of chemotherapy, steroids, surgery, and radiation. There are three key factors involved in determining treatment: neurologic deficit, patient factors, and spinal stability. A spinal instability neoplastic score is often used evaluate for spinal stability, with a score of 7 to 18 warranting surgical consultation.

Pain Bone metastases are the most common cause of cancer-related pain, although the majority of individual metastatic bone lesions are not painful [75]. Radiographs can identify lytic bone lesions as an area of radiolucency but only after a loss of 30% or more of bone mineral density; radiographs can be used as a screening tool, but continued clinical concern for a metastatic lesion in the presence of normal radiographs may warrant cross-sectional imaging. Unenhanced CT provides detailed bone anatomy and can be useful in the assessment of impending fracture risk or in preoperative planning. MRI provides very sensitive evaluation, identifying smaller nondestructive regions of marrow infiltration or metastatic disease [77]. Image-guided percutaneous cryoablation has proven effective for bone pain management. Radiofrequency ablation is an additional treatment option but may cause a temporary pain exacerbation.

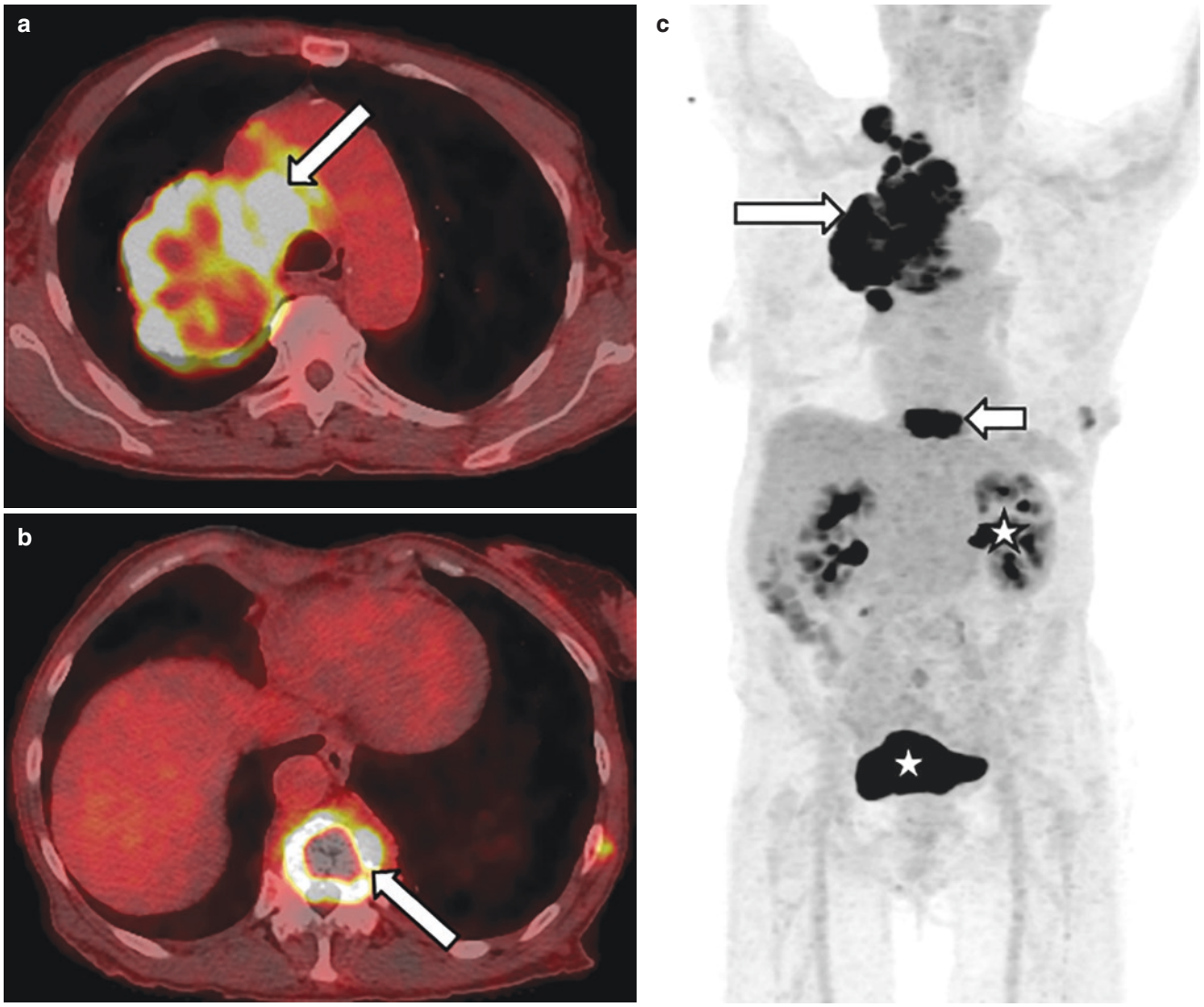

Fig. 46.20 *Case Study.* Imaging at follow-up patient encounter, 1 year later (**a**–**c**). Bright hot iron (*yellow/white*) color in axial fused FDG-PET/CT image indicates increased glucose (FDG) uptake in the highly metabolically active primary right hilar/right upper lobe malignancy. Bright hot iron color in (**b**) indicates metastatic lesion in the T12 vertebral body. Full-body three-dimensional FDG-PET projection in (**c**) demonstrates the primary tumor as a cluster of black masses (*long arrow*), vertebral metastasis (*short arrow*), and physiologic uptake in the renal collecting systems and urinary bladder due to excretion of FDG (*stars*). Metastatic right supraclavicular lymphadenopathy is demonstrated superior to the primary tumor

Hypercalcemia Hypercalcemia of malignancy comprises more than one-third of all cases of hypercalcemia presenting to the emergency department [47]. As many as one-third of cancer patients will experience hypercalcemia at some point in their disease course [25]. Hypercalcemia of malignancy can result from tumoral or systemic release of parathyroid hormone-related peptide (PTHrP), osseous metastases resulting in direct osteoclastic stimulation and osteolysis, and secretion of vitamin D analogues by the tumor [25, 47]. Radiologic manifestations of hypercalcemia of malignancy can include osteopenia and osteoporosis, resorption of bone at the distal clavicle and about the sacroiliac joints, and nephrocalcinosis and nephrolithiasis.

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Ultrasound

47

Sherwin Soltani, Konrad Karasek, Lamees M. Alshaikh, Ideen Zeinali, and Jennifer Carnell

Introduction

The use of bedside ultrasound by trained physicians has advanced the practice of medicine. Over the past two decades, clinician-performed ultrasound has seen widespread adoption as a core skill in emergency medicine and critical care medicine [1, 2]. With appropriate training and a symptom-based approach, emergency ultrasound is field-tested in the rapid diagnosis and management of undifferentiated critically ill patients [3–5]. The numerous emergencies associated with cancer and its treatment, including septic shock, ascites, pleural and pericardial effusions, pulmonary embolism, deep venous thrombosis, and bowel obstruction, among others, can all be diagnosed with bedside ultrasound, helping the clinician focus their initial differential diagnosis, thus decreasing time to diagnosis and stabilization.

Bedside ultrasound, also known as point-of-care ultrasound (POCUS), emergency ultrasound, or clinical ultrasound, is an extremely broad topic, and the interested reader is encouraged to learn more about this topic through the many available resources in textbooks and free-and-open access medical education.

Basic Ultrasound Functionality

An ultrasound machine is always paired with a transducer that is applied to the patient's skin. The transducer contains piezoelectric crystals or a specialized transducer-on-chip that vibrates when electricity is applied to it, generating ultrasound waves typically in the range of 2–15 MHz that are conducted through the body through a coupling medium such as gel [6, 7]. Soft tissue, blood, simple fluid, fat, bone, and air all conduct these ultrasound waves with slightly different velocities and impedance, producing reflections that travel back to the transducer. These reflections are processed by the machine based on how long they take to return, where on the ultrasound array they are heard, how strong they are and their frequency, to produce a 2D representation called a B-mode image (Fig. 47.1a) [7, 8].

Bright or hyperechoic areas of B-mode images represent stronger reflectors of ultrasound waves such as bone. Dark or hypoechoic areas of the image are the result of weaker reflectors. Areas where there are no ultrasound wave reflections, as seen with fluid, are termed anechoic and appear black on the ultrasound screen. The resolution of an ultrasound image is a function of the machine's sensitivity and the frequency used to generate the image. Higher frequency ultrasound waves produce higher resolution images at the cost of decreased depth of penetration, while lower frequency ultrasound can image deeper structures but sacrifices resolution.

Modern ultrasound machines incorporate other functionality. M-mode images such as Fig. 47.1b are formed by taking a single "slice" of a B-mode image and graphing motion within that slice over time and are useful for imaging salient parts of rapidly moving structures, such as the heart [8]. Doppler imaging, so named for the physics concept behind the technology, measures the difference in returned ultrasound frequency to determine the velocity of fluid within the image. Color Doppler imaging (Fig. 47.1c) employs color over a grayscale image to indicate direction of flow within a structure, while spectral Doppler measures precise flow velocities and direction of flow within a structure.

Ultrasound Transducer Selection

Ultrasound transducers vary in their frequency range and the method they use to steer ultrasound waves. Usually, these transducers are marked on one side with a transducer marker, which may be a small notch or coloration. This corresponds to a dot or

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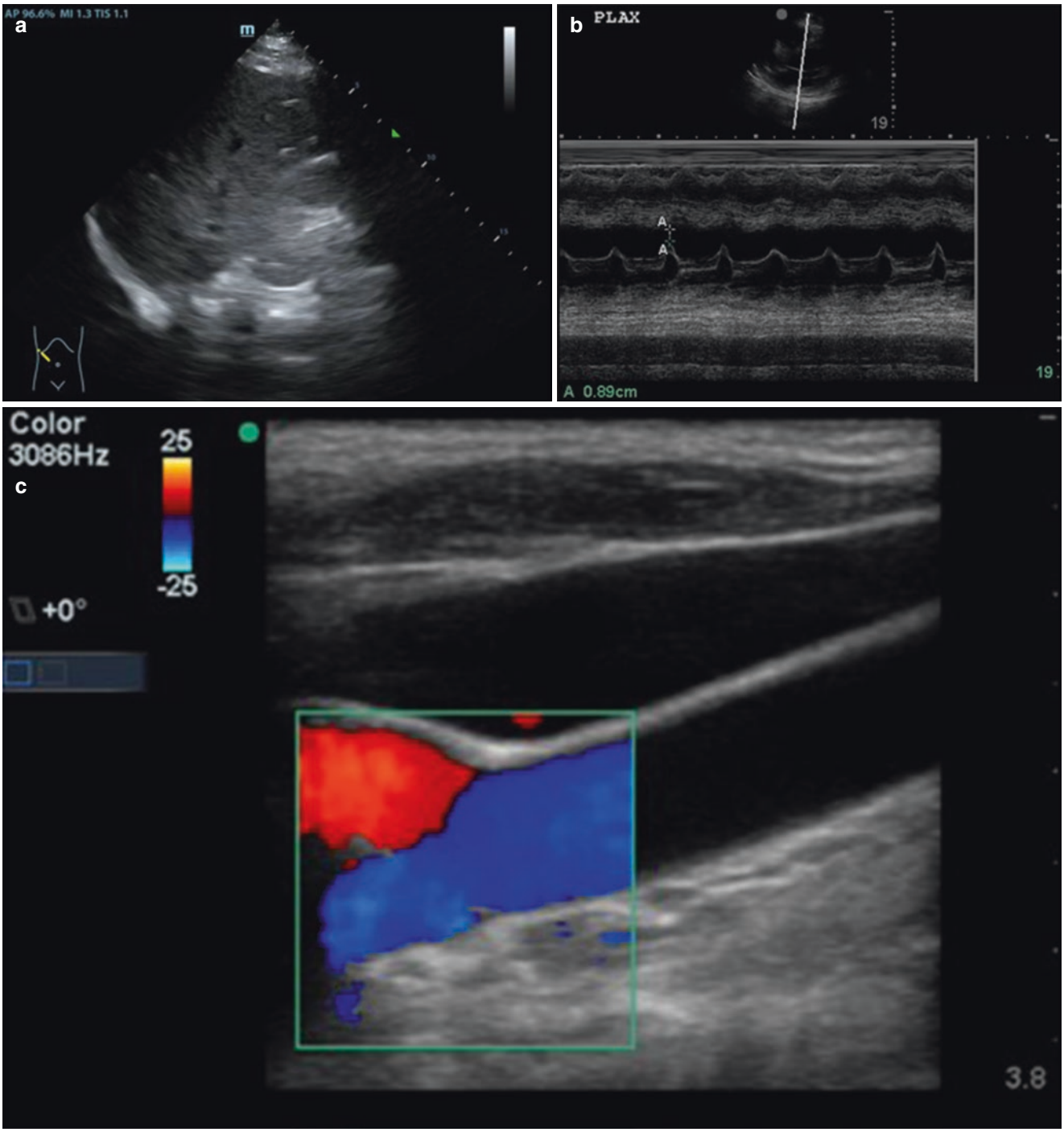

Fig. 47.1 Ultrasound imaging modes. (**a**) B-mode, also called 2D mode on some machines, produces 2D image of echo-producing interfaces of underlying objects. (**b**) M-mode, "motion mode," demonstrates movement of structures over time. All cardiac structures through which the solid white line passes in the top B-mode image are graphed over time in the bottom M-mode image. With this mode, precise measurements can also be made. (**c**) Color Doppler mode shows the direction of blood flow in a color map superimposed on this 2D image of the bifurcation of the common carotid artery

another marker on the ultrasound machine display, allowing the operator to anatomically orient their image on the screen.

Linear array transducers (Fig. 47.2a), as their name implies, use crystals arranged in a line, firing sequentially to produce an image which represents a slice of the overall area being imaged [6]. These high-frequency transducers produce images with excellent resolution but have limited depth of penetration. Consequently, they are primarily used for imaging superficial structures or masses, evaluating veins for thrombosis or for real-time procedural guidance.

Fig. 47.2 Commonly employed ultrasound transducers. (**a**) Linear array transducer (high frequency, 4–12 MHz), (**b**) curvilinear array transducer (low frequency, 1–5 MHz), and (**c**) phased-array transducer (low frequency, 1.5–4 MHz)

Curvilinear arrays are convex-shaped crystal arrays (Fig. 47.2b). Their larger footprint creates a wider field of view, allowing them to evaluate larger organs more easily. These transducers typically have lower frequency output and are suitable for imaging the abdomen, thorax, or deeper extremity structures.

Phased-array transducers (Fig. 47.2c) have a smaller footprint. Instead of using long arrays of crystals, a smaller number of crystals are instead pulsed in specific timing sequences that allow the beam to be steered electronically. These transducers produce pie-shaped images that are similar to curvilinear arrays. A significant advantage of their reduced footprint is that it allows imaging of areas of the body where acoustic windows are limited due to underlying air or bone, most notably in cardiac imaging. Phased-array transducers are also capable of general abdominal and thoracic imaging.

Endocavitary transducers commonly produce midrange ultrasound frequencies and are arranged as a highly convex curvilinear array. In combination with appropriate institutional protocols for high-level disinfection and sterile trans-

ducer covers, these transducers can be used for obtaining intraoral, transvaginal, or transrectal images that can aid in the visualization of certain organs or pathologies.

Adjusting the Ultrasound Image

On most machines, the operator has direct control over the depth, gain, and the imaging preset or resolution. Machines vary in their capabilities for more advanced functionality, such as Doppler imaging, M-mode imaging, zooming, frequency adjustment, or harmonic imaging. Depth has a dedicated control and is indicated to the side of the image by hash marks, and often the maximal depth is displayed numerically next to the image. Gain controls how bright or dark the image appears on the screen and can be adjusted for the entire image at once or can be adjusted at certain depths, depending on the machine's capabilities, a function called time gain compensation (TGC) [7].

Most ultrasound machines have imaging presets, for example, an abdominal, cardiac, or vascular mode. Presets may adjust frequency settings, output power, image post-processing, or the frame rate to help optimize the images displayed.

Safety of Bedside Ultrasound

The amount of ultrasound energy that is imparted during an exam should be minimized in accordance with the ALARA principle. Although ultrasound does not use ionizing radiation, ultrasound waves can induce effects such as cavitation, causing local tissue damage or thermal heating. These effects are displayed by the machine in terms of mechanical index (MI) and thermal index (TI), respectively, usually as unitless numbers. In general, the lowest numbers achievable with the shortest duration of imaging minimize the potential for adverse effects [8]. Tissue heating and mechanical disruption are of most concern for obstetric imaging and for imaging of the eye.

Other safety considerations include infection control, the need for sterile probe cover use during invasive procedures, and guidelines for disinfection of transducers, all of which are usually established by local institutional guidelines and protocols.

Emergency Cardiac Ultrasound

Basic Approach

There are four essential views for transthoracic cardiac ultrasound: the parasternal long axis, the parasternal short axis, the apical four chamber, and the subxiphoid. A small footprint phased-array transducer is used with the cardiac preset and a depth of 16–20 cm. A curvilinear array transducer may be used if the phased-array transducer is not available.

For the parasternal views, the transducer marker is aimed toward the right shoulder or the right hip for the long and short axis, respectively. In the apical four-chamber and the subxiphoid views, the transducer marker is aimed toward patient's right (Fig. 47.3). Cardiac visualization may be improved by placing the patient in the left lateral decubitus position and instructing the patient to hold their breath after exhaling. The subxiphoid view may be improved by having the patient flex their hips and knees and inhale slightly.

Pericardial Effusion and Cardiac Tamponade

Ultrasonography is the imaging modality of choice for detecting pericardial effusions and tamponade, common abnormalities found in oncologic patients, which may be a consequence of the underlying cancer diagnosis [9] or secondary to chemotherapy [10, 11]. In the normal heart, the pericardium appears as a hyperechoic outline of the more hypoechoic myocardium. A pericardial effusion appears between these two layers [12, 13]. An effusion with simple fluid typically appears as an anechoic stripe (Fig. 47.4; see Fig. 47.4b). However, complex malignant, exudative, or hemorrhagic effusions may have hyperechoic portions or contain septations.

The pericardial fat pad may mimic a small pericardial effusion. Frequently, this more solid component appears to contain internal echogenicity and moves with the epicardium to which it is attached in time with the cardiac cycle. Multiple cardiac views may be necessary to differentiate pericardial fat from an effusion [12].

Pericardial effusion is best detected in the subxiphoid and parasternal views by interrogating the most dependent potions of the pericardial sac where fluid is expected to collect first. The most dependent area in the subxiphoid view lies anterior and adjacent to the right ventricle and, in the parasternal views, lies along the posterior aspect of the pericardial sac, just anterior to the descending thoracic aorta (see Fig. 47.4b) [13]. In the apical view, fluid may appear anywhere circumferentially. While fluid in the pericardial sac preferentially collects in the most dependent area, in complex malignant, exudative, or hemorrhagic effusions, fluid may defy this rule and collect in nondependent areas.

Cardiac tamponade is a crucial diagnosis as it is a potentially reversible cause of shock. POCUS allows the real-time visualization of the effects of increased intrapericardial pressure on the heart. The right side of the heart typically

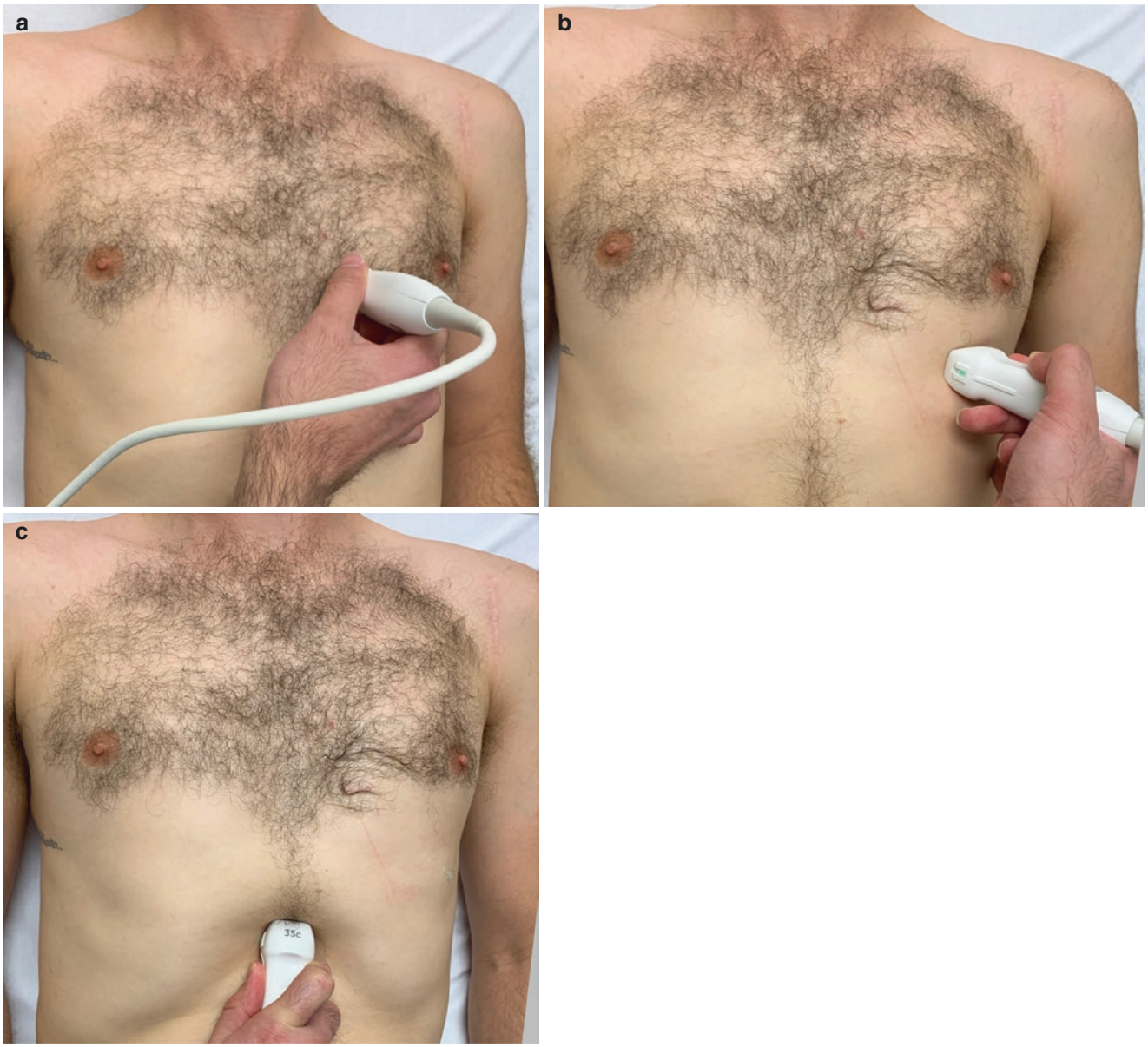

Fig. 47.3 Transducer placement for cardiac views. (**a**) Parasternal views, transducer normally placed in the fifth intercostal space to the left of the sternum. For the parasternal long-axis view, the transducer marker is oriented to the right shoulder, and for the short-axis view, it is rotated 90° to the right hip. (**b**) Apical view, with the transducer marker to the patient's right, typically placed at the midclavicular line at the level of the nipple line or at the mammary fold in female patients. (**c**) Subxiphoid view, with the transducer marker to the patient's right, transducer placed under the xiphoid process, aimed slightly to the left hemithorax

has the lowest intracardiac pressure and thus is affected first. The right ventricle (RV) and right atrium (RA) are best visualized in the apical four-chamber or subxiphoid views [12, 14]. Inversion of the RA occurring during systole (Fig. 47.5a), when atrial filling should occur, is the most sensitive, though least specific, sign of cardiac tamponade. As pericardial pressure increases, RV free wall inversion (RVI) can be noted during diastole (Fig. 47.5b) [12, 14]. M-mode imaging is of utility, as most patients with tamponade are tachycardic, making visual detection of signs of tamponade challenging. By positioning the cursor through the mitral valve (MV) leaflets and the RV free wall (Fig. 47.5c), diastole can be identified as the portion of the cardiac cycle when the MV leaflets are open and concurrent RVI may be detected (Fig. 47.5d).

In tamponade, elevated central venous pressure results in a dilated IVC that has minimal respirophasic variation.

In the rapidly deteriorating patient, derangement of vital signs may preclude in-depth cardiac examination, and a finding of pericardial effusion with clinical symptoms of tamponade should prompt emergent intervention by the clinician.

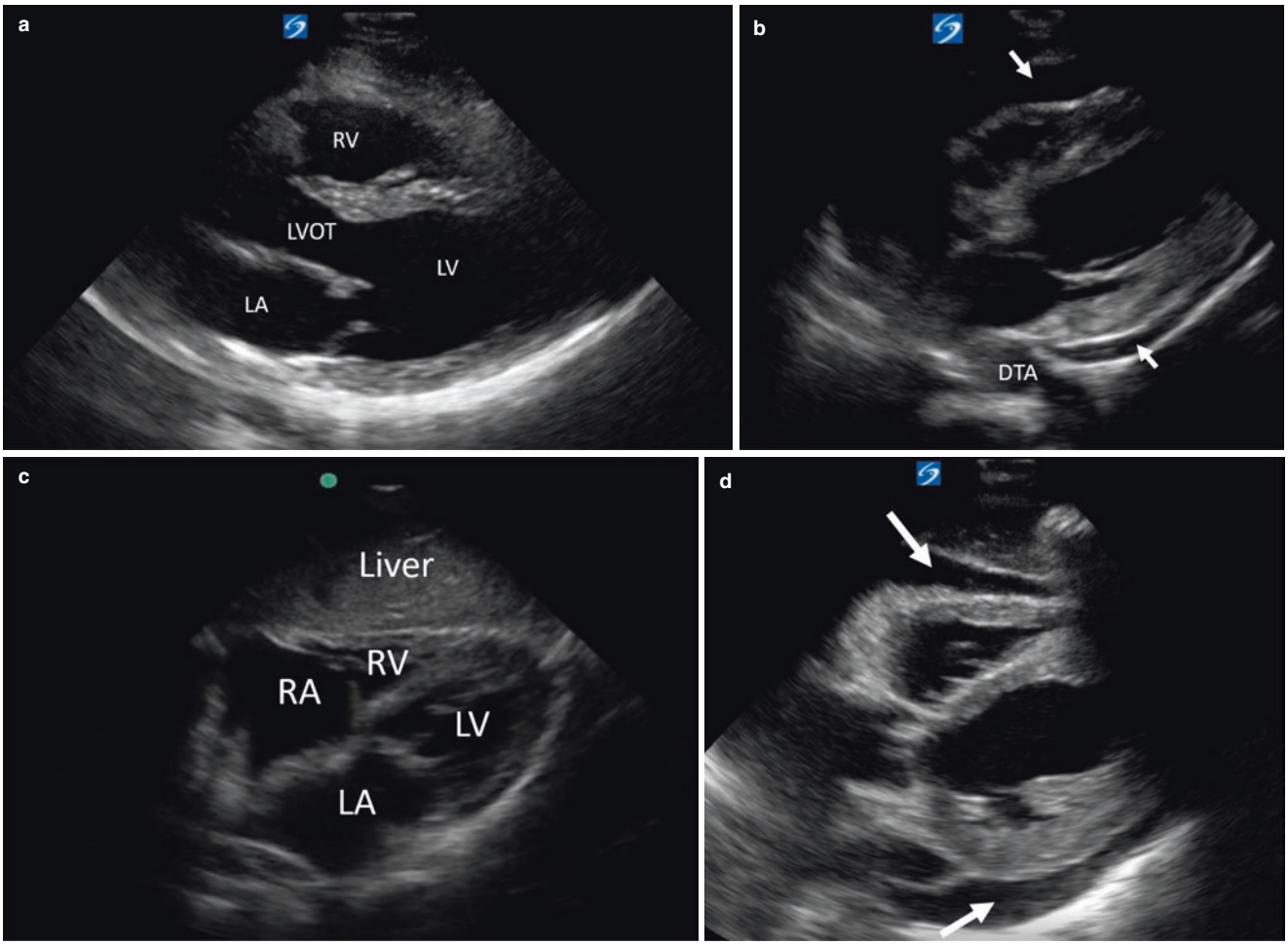

Fig. 47.4 Parasternal and subxiphoid views of the heart. (**a**) Normal parasternal long-axis view. (**b**) Parasternal long axis with circumferential pericardial effusion (*arrows*). (**c**) Normal subxiphoid view. (**d**) Subxiphoid view with effusion (*arrows*). LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; RA, right atrium; RV, right ventricle; DTA, descending thoracic aorta

Left Ventricular Function

Left ventricular systolic function can be rapidly estimated by a bedside echocardiogram. In the normal left ventricle (LV), there is simultaneous inward movement and thickening of the ventricular septal and free walls during systole (Fig. 47.6). Dilation, myocardial thinning, and poor contractility may all be observed in heart failure. Various methods of measuring the LV cavity size are known; however, visual estimation of the LV systolic function by emergency physicians skilled in bedside ultrasound has been shown to be comparable in performance to advanced measurements and estimation by cardiologists [15].

In patients without LV systolic impairment or MV disease, the MV opens briskly during early diastole, and the anterior leaflet, easily seen on the parasternal long-axis and apical views, moves toward the septal wall. The point at which the anterior MV leaflet is the closest to the septum is called the E-point, and the distance between the anterior MV leaflet and the septal wall is the E-point septal separation (EPSS). An EPSS of greater than 7 mm is highly sensitive for decreased LV systolic function, and in general the greater the EPSS, the worse the LV ejection fraction (LVEF) [16, 17]. The use of EPSS as an indicator of LV systolic function has not been validated in patients with valvular disease of the mitral or aortic valves, where impaired valve mobility may lower EPSS independent of LV function.

Right Ventricular Strain

Pulmonary embolus (PE) is one of the leading complications of malignancy and remains high on the differential of the cancer patient presenting with acute chest pain, shortness of breath, or hypotension. Massive or sub-massive PEs are a cause of obstructive shock and rapid decompensation [18].

With POCUS, the RV is best evaluated in the apical four-chamber view. RV dilation is variably defined; however, a

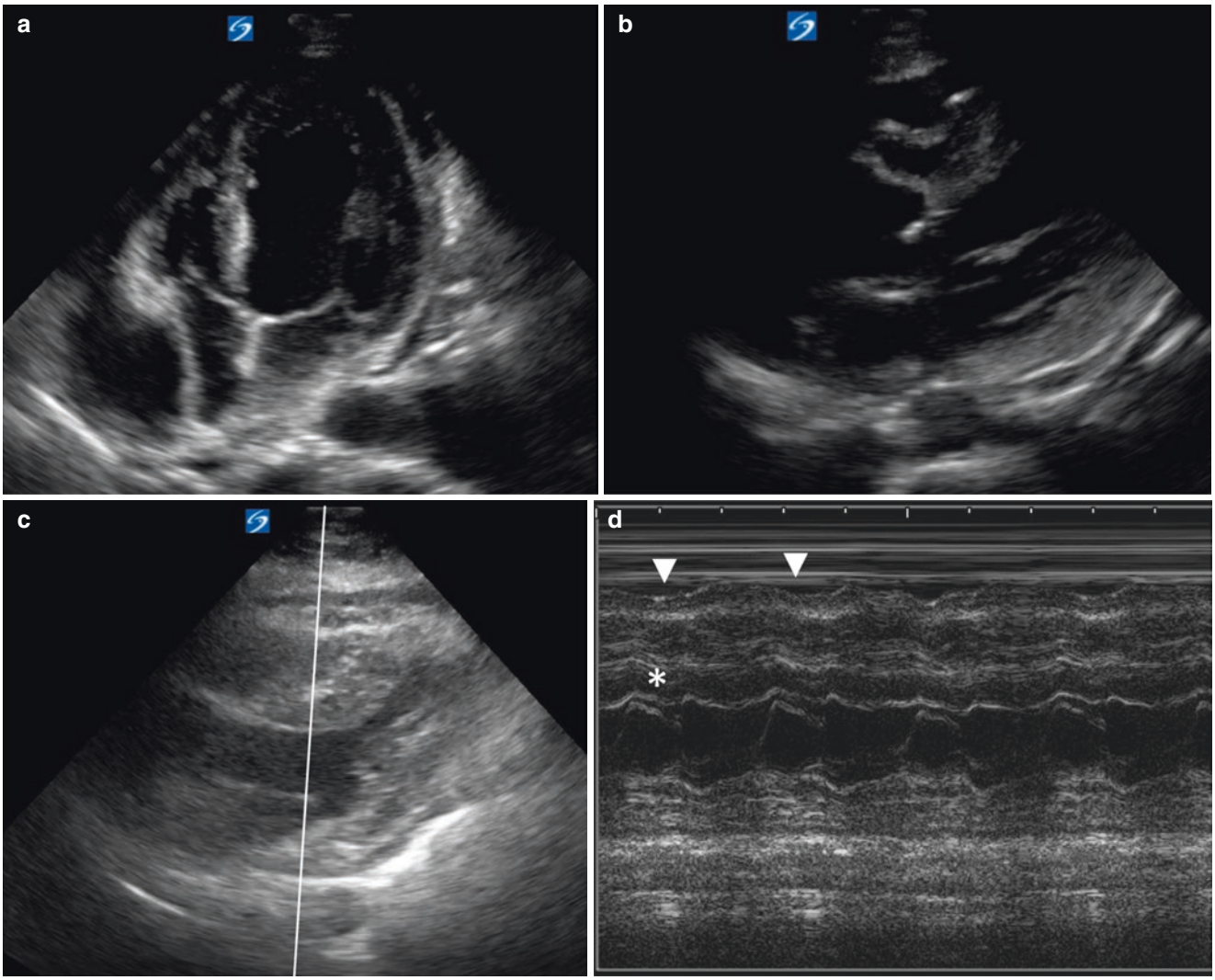

Fig. 47.5 Echocardiographic signs of tamponade. (**a**) Right atrial inversion (RAI) seen during systole (MV closed) in the apical four-chamber view, a more sensitive but less specific sign. (**b**) Diastolic right ventricular inversion (RVI), a more specific sign of cardiac tamponade. (**c**) M-mode through the anterior mitral valve leaflet and RV outflow tract in the parasternal long-axis view, with (**d**) showing the resulting M-mode tracing. When the MV is open (*) in diastole, there is inward movement of the RV free wall (*arrowhead*)

ratio of RV/LV >0.9 is considered abnormal [19, 20]. In the normal parasternal short-axis view, the LV has a uniform circular shape, with the septum pushed outward into the RV due to the higher chamber pressure within the LV relative to the RV.

In the setting of RV strain, there is dilation of the right ventricle. The increasing pressure within the RV can manifest as septal flattening, where the normal curvature of the septum into the RV is lost. This finding is known as the "D-sign" on the parasternal short-axis view and will initially be seen in diastole but progress to be present throughout the entire cardiac cycle (Fig. 47.7; see 47.7a). On the apical four-chamber view, RV free wall hypokinesis with relatively preserved apical motion, a finding known as McConnell's sign, may be seen [21]. Anterior movement of the tricuspid annulus during RV systole, a measurement known as tricuspid annular plane of systolic excursion (TAPSE), is a good surrogate for RV systolic function in the typical adult heart (Fig. 47.8) [22]. This can be measured using an M-mode cursor through the junction of the tricuspid annulus and the RV free wall. In general, an abnormal TAPSE is <17 mm [22], and in confirmed PE, TAPSE <15 mm confers increased risk of mortality or need for thrombolysis [19, 20]. Interrogation of the IVC may reveal dilation without respirophasic variation, suggestive of increased central venous pressure.

Measurement of the Inferior Vena Cava

The inferior vena cava (IVC) can be seen from a subcostal approach as it courses posterior to the liver before passing above the diaphragm. From a subxiphoid view of the heart,

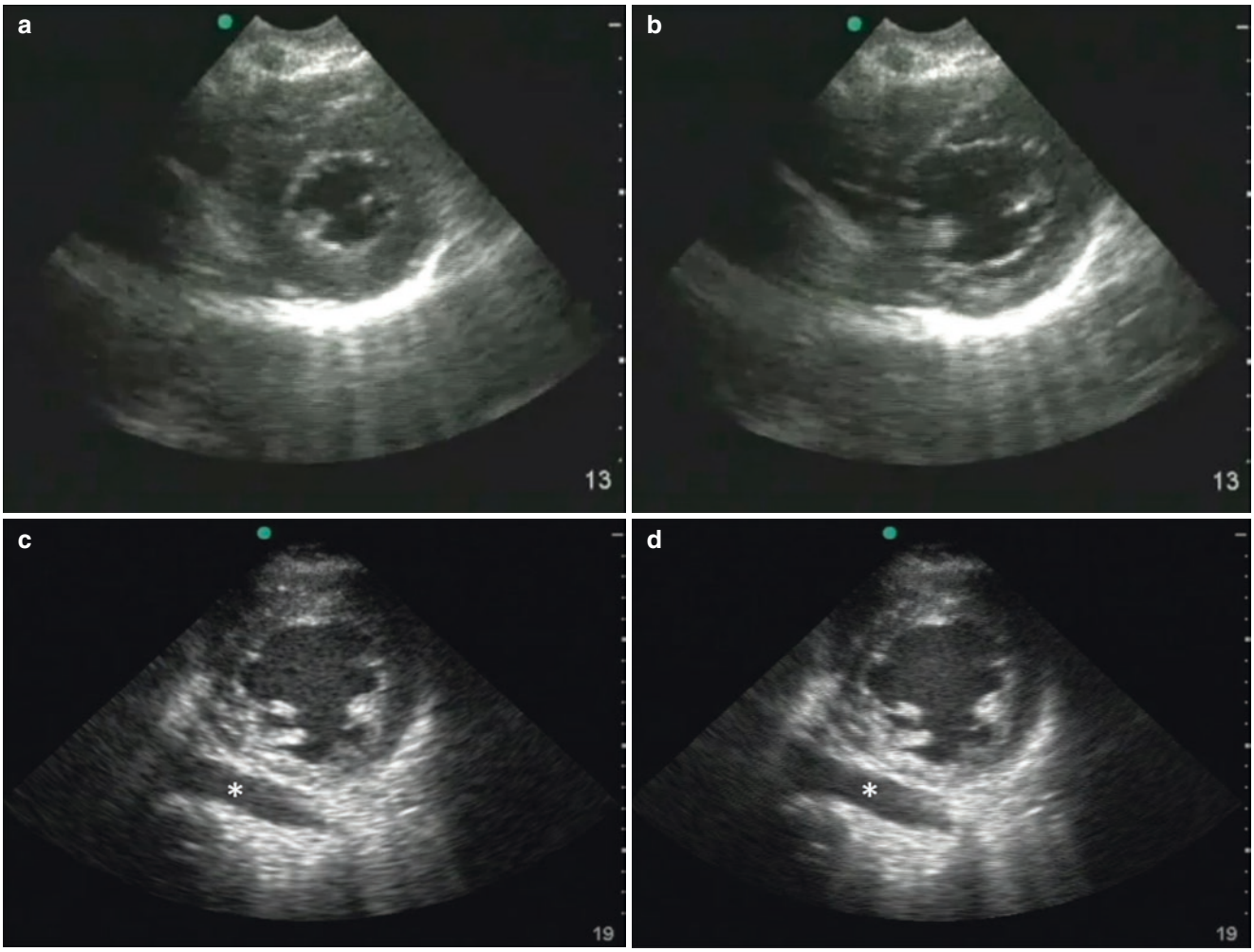

Fig. 47.6 Left ventricular ejection fraction evaluated in the parasternal short axis. (**a**, **b**) End systole and end diastole in a normal heart. (**c**, **d**) End systole and end diastole, with markedly reduced wall contraction resulting in little to no change in the left ventricular size. (*) Small left pleural effusion

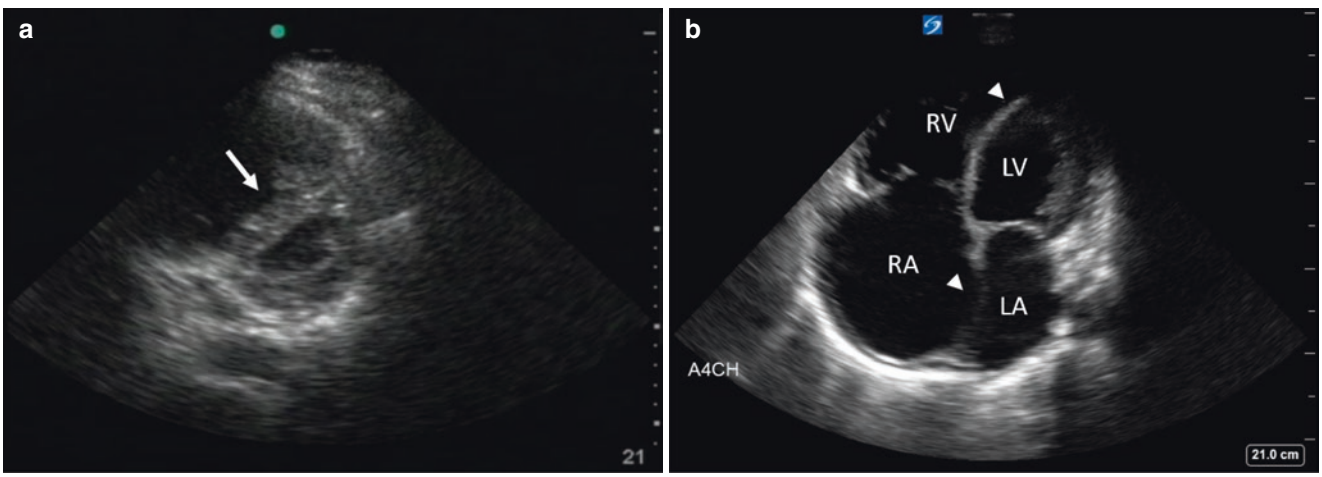

Fig. 47.7 Elevated RV pressure resulting in echocardiographic changes. (**a**) The "D-sign": RV strain produces septal flattening (*arrow*) on the parasternal short-axis view, which results in a loss of the typical cylindrical shape of the LV. (**b**) RV and RA dilation in the setting of elevated right heart pressures. In end diastole, the RV cavity size measured near the base is larger than the LV size, and the septum is pushed toward the left heart (*arrowheads*)

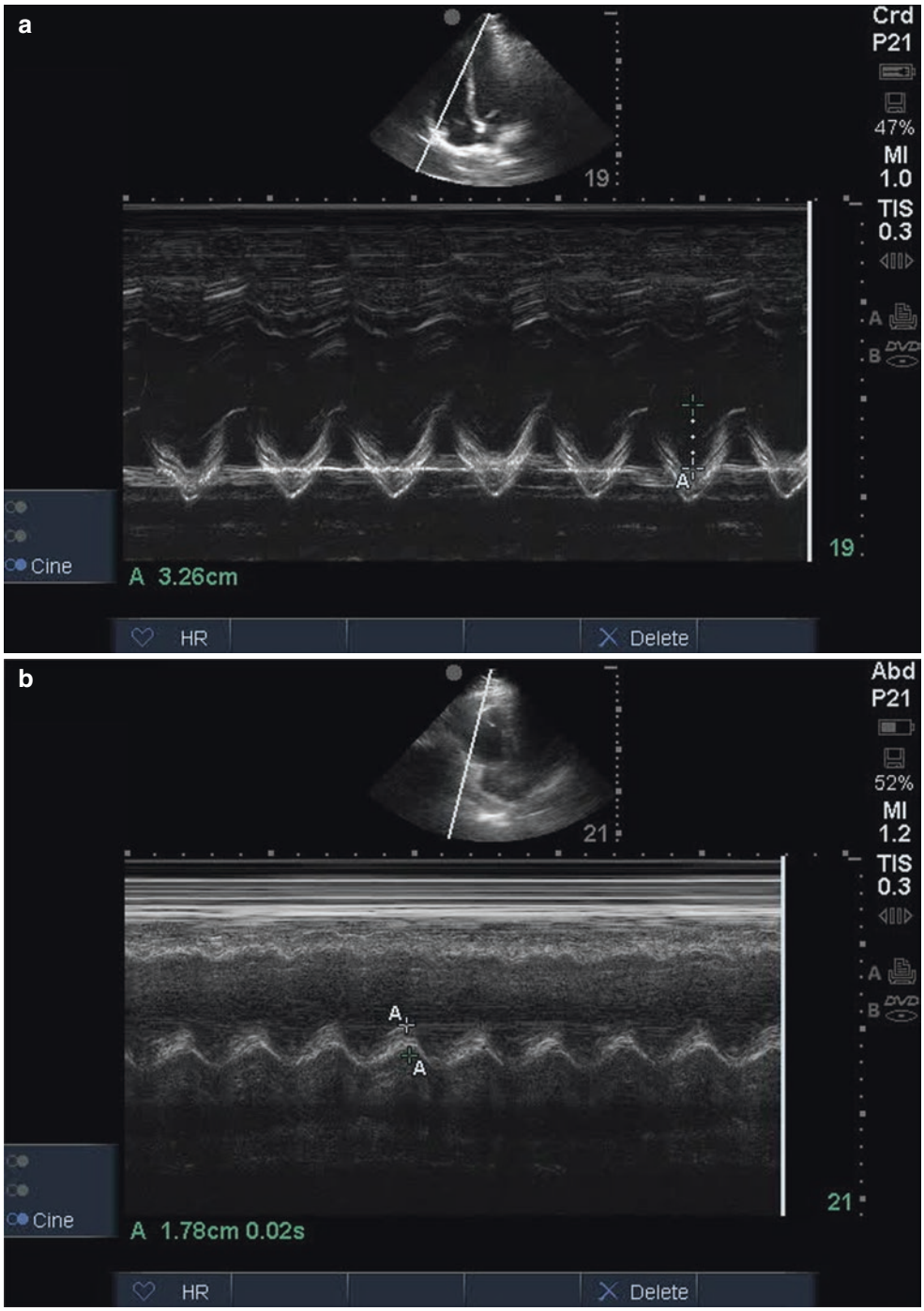

Fig. 47.8 Tricuspid annular plane systolic excursion (TAPSE) measurement. The M-mode cursor is positioned through the junction of the tricuspid annulus and RV free wall in the apical four-chamber view. The resulting M-mode tracing is measured peak to trough. (**a**) Normal TAPSE (32 mm). (**b**) Decreased TAPSE in a patient with acute right heart strain (17 mm)

the transducer should be fanned posteriorly until the IVC is identified near its junction with the right atrium. The transducer can then be turned to a long-axis view with the transducer marker cephalad. Direct visualization of the IVC in the supine, spontaneously breathing patient, assuming there is no IVC obstruction or altered anatomy, correlates to a limited extent with the central venous pressure (CVP) or right atrial pressure (RAP). Respirophasic variation in the IVC size is due to changes in intrathoracic pressure caused by the respiratory cycle.

CVP or RAP can be inferred either from the maximal IVC size (IVCmax; measured inferior to the hepatic vein) or from the percent change in size with inspiration $\left(\frac{IVCmax - IVCmin}{IVCmax}\right)$, also known as collapsibility index (CI). Significant heterogeneity in research methods used by studies to correlate CVP to IVCmax or CI exists, though guidelines suggest that IVCmax >2.1 cm with CI < 0.50 (with sniffing maneuver) suggests an approximate RAP of 15 mmHg [22, 23]. More qualitatively, a dilated IVC with

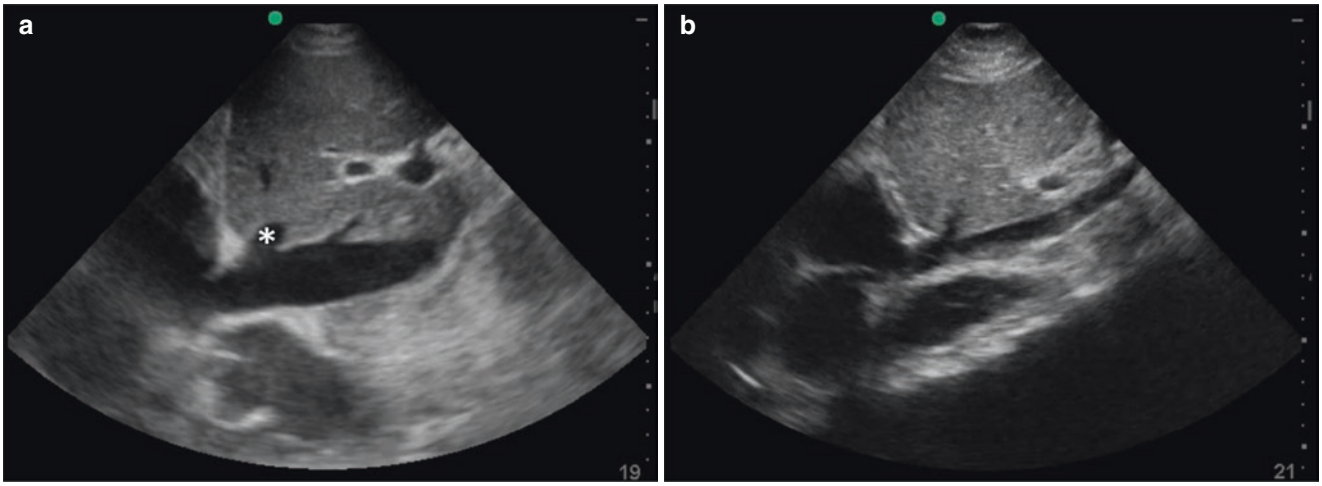

Fig. 47.9 Measurement of the inferior vena cava in the subcostal view. The liver overlies the IVC, and typically the hepatic vein can be seen emptying into the IVC (*). (**a**) Dilated IVC measuring greater than 2 cm, with low respiratory phasic variation (almost no collapse with inspiration) and thus a low collapsibility index (CI). The CVP in this patient is likely elevated. (**b**) Small IVC with CI of greater than 0.50, suggesting normal CVP

little respiratory variation may be seen in obstructive pathologies such as cardiac tamponade, pulmonary hypertension/PE, RV failure, or tension pneumothorax (Fig. 47.9).

Thoracic and Pulmonary Oncologic Emergencies

POCUS allows medical providers to perform real-time, bedside evaluation of undifferentiated oncologic patients with respiratory symptoms in the emergency department. It is rapid, reproducible, and often more sensitive and specific than a radiograph.

Lung ultrasound can be performed with any of the commonly accessible transducers – curvilinear, phased-array, or linear – and selection will depend on the specific application as well as provider preference. For most applications, a low-frequency curvilinear or phased-array transducer is best suited for detecting oncologic emergencies. Conventionally, the transducer marker is either oriented to the patient's right or toward their head. The exam mode should utilize the "pulmonary" or "lung" preset, and the depth of the image should be set to at least 18 cm. If a "lung" preset is not available, an "abdominal" preset is appropriate.

Zones of the Lung

Each hemithorax is divided into four distinct areas, for a combined eight zones on the anterolateral chest (Fig. 47.10). The lung assessment should be performed in a systematic and comprehensive manner. With the patient

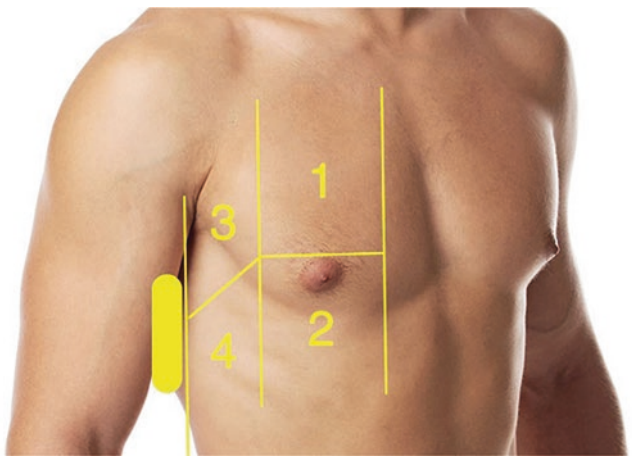

Fig. 47.10 Each hemithorax is divided into four distinct areas, for a combined eight zones on the anterolateral chest. Each field should be interrogated as part of the lung ultrasound exam. The PLAPS point (posterolateral alveolar and/or pleural syndrome) is the area where most pneumonias and consolidations will be visualized

supine or semi-recumbent, each hemithorax should be imaged in a sagittal orientation, with the transducer marker toward the patient's head. Landmarks include the pleural line (parietal and visceral pleura) and the lung parenchyma flanked by the ribs and their corresponding posterior acoustic shadowing. The angle of insonation should be manipulated to optimize the clarity of the pleural line (Fig. 47.11). Experts also recommend imaging the posterolateral alveolar and/or pleural syndrome (PLAPS) point, where most pneumonias and consolidations will be visualized [24, 25].

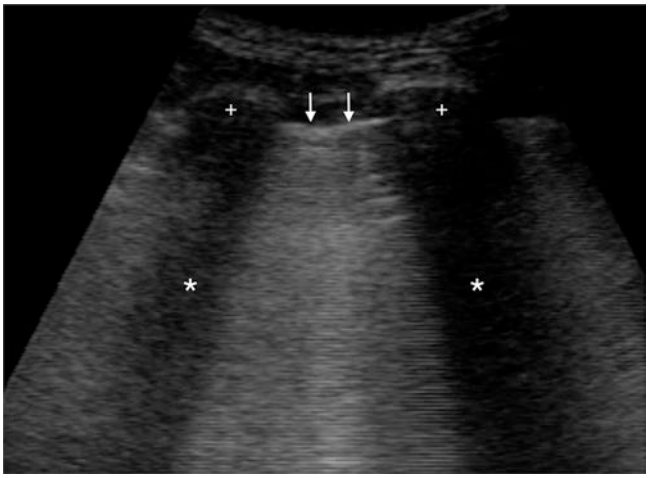

Fig. 47.11 The pleural line (*arrows*) appears as a bright hyperechoic line separating the superficial soft tissue from the lung parenchyma. The pleural line is flanked by hyperechoic ribs (+) with posterior acoustic shadowing (*). Utilizing an angle of insonation perpendicular to the pleural line will improve visualization of relevant findings. Lung sliding appears as a shimmering artifact at the pleural line and corresponds with the respiratory cycle

Lung Artifacts (A-Lines and B-Lines)

In normally aerated lung, there are linear, echogenic, horizontally oriented reverberations generated from the pleural line. These reverberation artifacts are called A-lines [26–28]. While A-lines are seen in normal lung, they are also seen in the setting of lung pathology such as chronic obstructive pulmonary disease (COPD), asthma, and pneumothorax. In contrast, B-lines are hyperechoic, discrete, vertical beams of artifact that generally obliterate A-lines, extend to the bottom of the screen, and move in synchrony with the patient's pleural line [26, 27]. B-lines represent increased density in the lung parenchyma and, depending on the clinical context, can be diagnostic of multiple pathologies relevant to malignancy, including tumor, pneumonia, pneumonitis, lung infarction, and fibrosis, among others (Fig. 47.12).

Diffuse Interstitial Syndrome

Looking in each of the eight scanning zones, a zone is positive if it has three or more B-lines at any point in a respiratory cycle. The presence of two or more positive zones, on both hemithoraces, is consistent with diffuse interstitial syndrome (DIS) [26, 27].

In general, DIS is most often due to cardiogenic pulmonary edema in the setting of heart failure (HF). One study showed that the combination of LVEF <45%, a distended non-collapsible IVC, and presence of DIS is 100% specific for the diagnosis of acute decompensated HF [29]. However, it is important to note that this is not always the case as DIS itself is nonspecific and may represent other causes of dyspnea. In cases of DIS where the triad above are not found, one should consider other causes such as HF with preserved LVEF, acute respiratory distress syndrome (ARDS), pulmonary fibrosis, diffuse parenchymal lung disease, pneumonitis secondary to chemotherapeutic agents, or multifocal pneumonia secondary to immunocompromised state. Additionally, the presence of unilateral or focal B-lines may also indicate any of the following: pneumonia, atelectasis, mass, or infarctions (mostly due to pulmonary embolism). As with all POCUS, integration of the entire clinical picture by the operator improves the accuracy of the diagnosis.

Consolidation

Patients with malignancy are often on chemotherapeutic agents and medications that cause immunocompromised state, putting them at higher risk for infection. Oncologic patients presenting with dyspnea are at high risk for pneumonia, which account for approximately 10% of their hospital admissions, with rates as high as 30% in patients with hematologic malignancies [30]. Additionally, prior surgeries, radiation, infections, or compressive masses can cause recurrent post-obstructive pneumonia due to the patient's inability to clear static secretions in bronchi and alveoli distal to the obstruction. This leads to atelectasis and subsequent microbial colonization, infection, and consolidation [30].

Pneumonia occurs on a spectrum, depending on how much of the aerated lung is replaced with fluid, pus, or increased density. This can progress between various degrees of focal B-lines, atelectasis, subpleural consolidation, and, ultimately, *hepatization* (lung taking on a tissue-like appearance of solid organs, Fig. 47.13). The presence of subpleural consolidation is demonstrated as an irregular pleural line with hypodensities adjacent and just deep to it and may indicate an infectious process (this finding is known as the *shred sign*, Fig. 47.14). The presence of *static* and/or *dynamic air bronchograms* can help distinguish between atelectasis and pneumonia. Static air bronchograms are caused by the air that remains within the bronchi in a consolidative process and appear as nonmobile hyperechoic lines extending out to the periphery of the lung signifying complete bronchial obstruction. Static air bronchograms may be seen in resorptive atelectasis and pneumonia and, therefore, cannot be used to differentiate these pathologies (see Fig. 47.13). Dynamic air bronchograms are caused by hyperechoic air moving toward the periphery of the lung with inspiration [31]. Dynamic air bronchograms have a 94% specificity and a 97% positive predictive value for diagnosing pneumonia and distinguishing it from resorptive atelectasis [31].

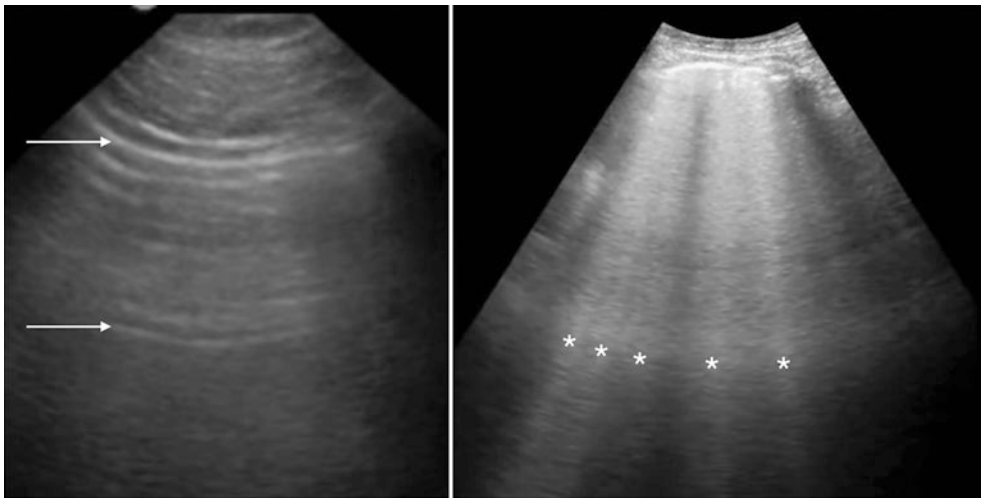

Fig. 47.12 A-lines are linear, equidistant, echogenic, horizontally oriented reverberation artifacts generated from the pleural line (*horizontal arrows*). B-lines result from increased density in the lung parenchyma and are hyperechoic, discrete, vertical beams that extend from and move with the pleural line, reaching a depth of 18 cm. B line artifacts (*) generally obliterate A-lines

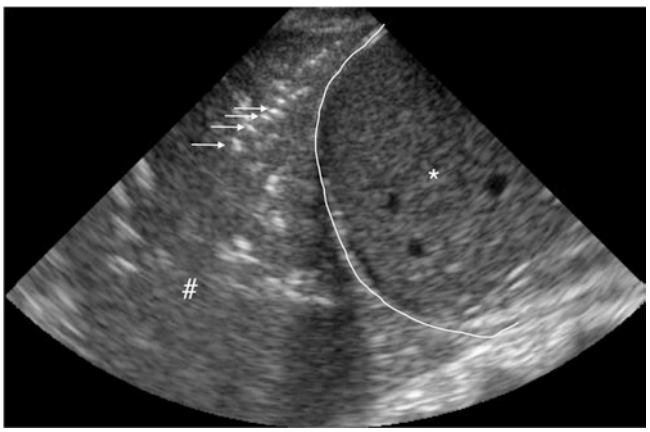

Fig. 47.13 Hepatization (#) represents highly consolidated lung parenchyma. It has similar echogenicity to the liver (*). The liver and consolidated lung are separated by the diaphragm (line). Within the consolidation, one can see static and/or dynamic air bronchograms (*arrows*)

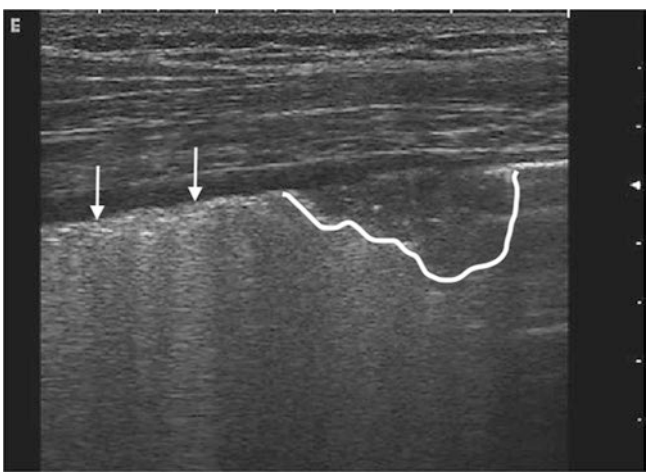

Fig. 47.14 Subpleural consolidation (*outlined*) is demonstrated as an irregular pleural line with subpleural hypodensities. It may indicate an infectious process. A normal pleural line (*arrows*) is also demonstrated here

Pleural Effusions

Pleural and parapneumonic effusions are common causes of dyspnea and chest pain in oncologic patients and have a significant effect on quality of life, often requiring frequent visits to the emergency department and procedures (i.e., thoracentesis) to help manage symptoms. While chest radiographs are traditionally used to diagnose effusion, POCUS is much more sensitive and specific, reliably identifying effusions as small as 20 mL, and is 100% sensitive for effusions >100 mL [32]. Pleural effusions are diagnosed by noting the absence of the mirror artifact (the echogenic reflection of the liver or spleen above the diaphragm) and by visualizing the spine sign (thoracic vertebral bodies extending cephalad past the diaphragm), which is approximately 93% sensitive and specific for detecting non-trace pleural effusions (Fig. 47.15) [33]. Effusions can be simple and anechoic, or complex and heterogeneous, sometimes mimicking consolidations or malignant effusions. POCUS can help distinguish whether the effusions are unilateral, bilateral, loculated, diffuse, simple, or complex. One study showed that ultrasonographic characteristics could help distinguish between transudative and exudative effusions. In this paper, they showed that transudates were *always* anechoic, whereas effusions with complex septated, complex non-septated, or homogeneously echogenic patterns were *always* exudative [34]. Additionally, POCUS can help identify relevant anatomy to help guide thoracentesis for recurrent malignant effusions and decreases the rate of pneumothorax from approximately 30% (landmark-based approach) to less than 3% [35].

Pleural Disease

The pleural line is best evaluated using the linear transducer, allowing for better resolution of the superficial structures.

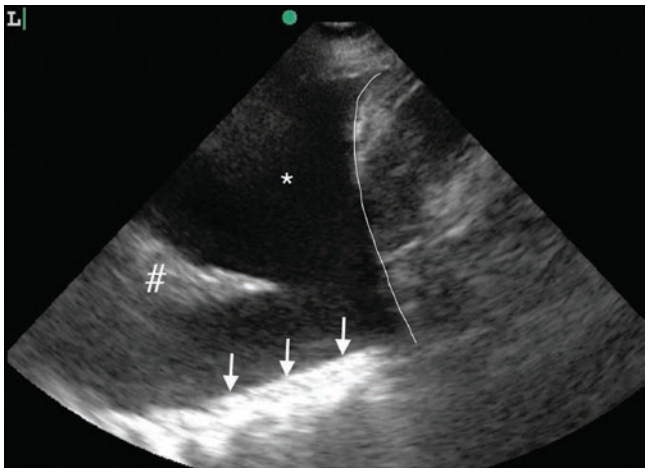

Fig. 47.15 This image shows an anechoic pleural effusion (*). Pleural effusions most commonly appear as anechoic collections above the diaphragm (line). Additional findings include absence of the mirror artifact (the echogenic reflection of the liver or spleen above the diaphragm) and the spine sign (visualization of thoracic vertebral bodies extending cephalad past the diaphragm) (*arrows*)

Normal pleura is smooth, hyperechoic, and thin (no more than 3 mm) [32]. The parietal and visceral pleura generally cannot be distinguished unless there is pathology present. Thickening can be caused by multiple etiologies, including infection and malignancy. Parietal pleura thickening >10 mm is predictive of malignancy [32]. Diffuse pleural irregularities are likely due to generalized processes like pulmonary fibrosis or pneumonitis, which may indicate an adverse reaction to chemotherapeutic agents in oncologic patients.

Pneumothorax

In patients with malignancy, iatrogenic causes (e.g., thoracentesis, biopsy, surgery) and the malignancy itself can cause pneumothorax. Approximately 10% of these patients will go on to have a malignancy-associated secondary spontaneous pneumothorax which is associated with increased morbidity and mortality [36].

POCUS is far superior to physical exam and chest radiograph for identifying pneumothoraces [37]. Pneumothoraces can be identified fairly quickly and easily with POCUS by placing a high-frequency linear transducer on the most superior portion of the anterior chest, with the transducer marker toward the head. Both sides of the chest should be evaluated. Start by looking for evidence of lung sliding between the parietal and visceral pleura. The appearance of lung sliding on ultrasound is best described as a "shimmering" of the pleural line or "ants crawling" along the pleural line and is produced by the apposed movement of the parietal and visceral pleura. Additionally, the presence of B-lines or comet tails at the pleural line is highly sensitive for ruling out pneumothorax [26, 27, 38]. The presence of lung point is the most specific (near 100%) for diagnosing pneumothorax [37].

Abdominal Oncologic Emergencies

Approximately 40% of cancer patients present to the emergency department with gastrointestinal symptoms [39]. POCUS can help evaluate for some of the more common pathologies.

Malignant Bowel Obstruction

Malignant bowel obstruction (MBO) usually results from mechanical obstruction caused by tumor burden, radiation-induced fibrosis, adhesive disease, or dysfunctional bowel motility. The incidence of MBO is approximately 3–15% of all patients with advanced cancer and occurs at all levels of the GI tract – gastric outlet, small bowel (most frequent), and large bowel [39].

In the supine position, a low-frequency curvilinear or phased-array transducer is used to scan the abdomen in both the transverse and sagittal planes, moving up and down the abdomen in the systematic lawn-mower pattern from one lower quadrant to another. The presence of a small bowel obstruction (SBO) is detected by identifying dilated (>2.5 cm, most sensitive), noncompressible, loops of bowel with the presence of back-and-forth movement of intraluminal contents (most specific, Fig. 47.16). Additional evidence of a bowel obstruction can be indicated by an increase in bowel wall thickness (>3 mm) or the presence of localized intraperitoneal free fluid tracking between the loops of bowel (*tanga sign*). POCUS is between 91–98% sensitive and 93–98% specific, for the diagnosis of SBO when performed by providers with minimal training [40, 41]. Large bowel obstruction has similar features but is generally dilated to >5.0 cm.

Ascites and Perforation

One of the most common complications that providers will encounter will be the presence of malignant ascites or free fluid in the abdomen – usually secondary to hepatobiliary, gynecologic, or metastatic malignancies. Specific views include the space between the liver and kidney (hepatorenal space or Morison's pouch), the area around the spleen (perisplenic space), and the area around and behind the bladder (retro-vesicular/rectovaginal space or pouch of Douglas) – these are components of the well-known FAST exam (focused assessment with sonography in trauma) [28]. A dark or anechoic area in any of these three potential spaces

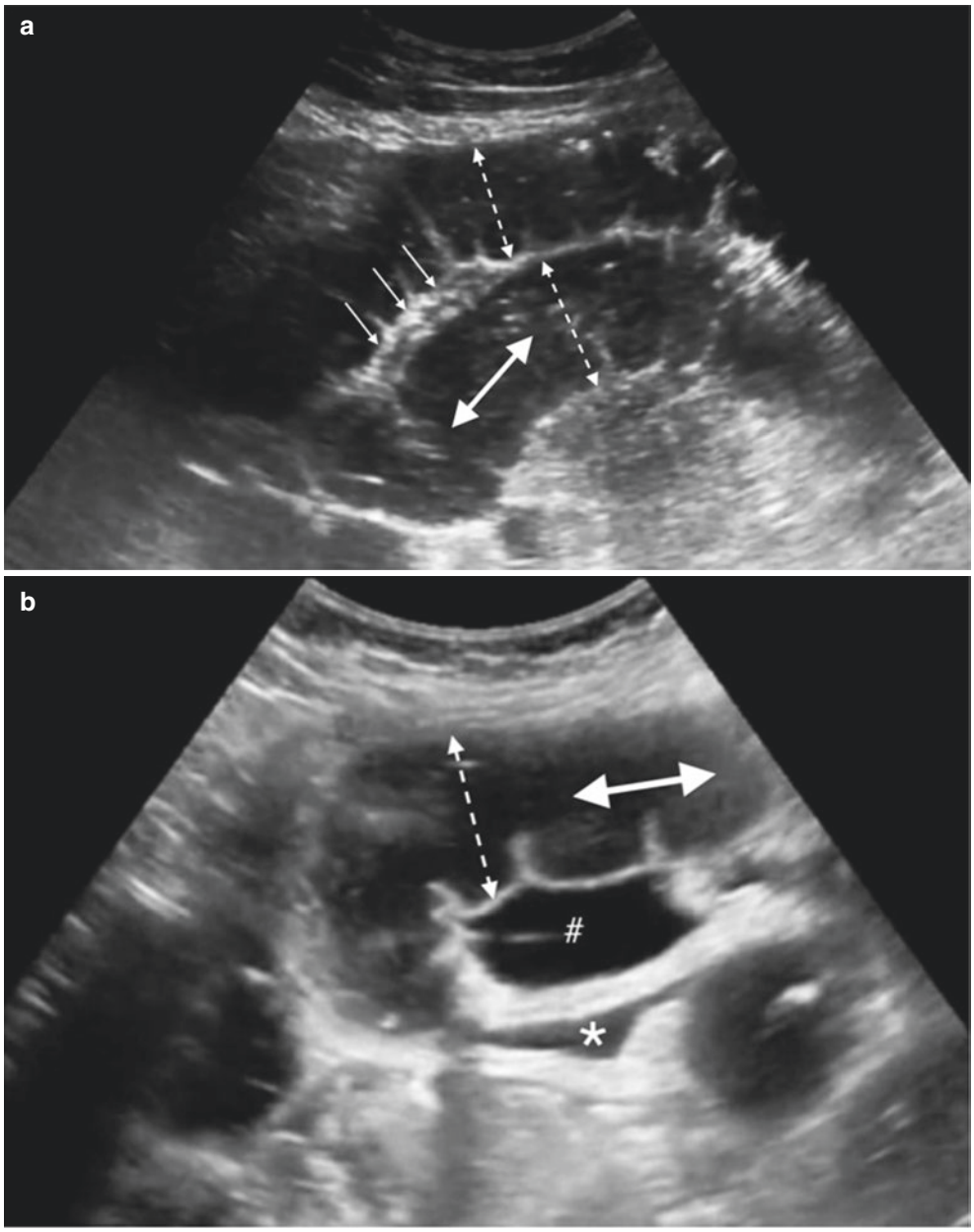

Fig. 47.16 Examples (**a**) and (**b**) of a small bowel obstruction (SBO). An SBO is detected by identifying dilated (>2.5 cm, most sensitive, double-headed dashed line), noncompressible loops of bowel with the presence of intraluminal contents without visible forward movement with peristalsis ("to-and-fro peristalsis," most specific, *solid double-headed arrow*). Additionally, increased bowel wall thickening, >3 mm (small *arrows*) (**a**), and localized free intraperitoneal fluid (#) or fluid tracking between the distended loops ("tanga sign") may also be seen (*) as in (**b**)

indicates free intraperitoneal fluid, which may represent ascites, blood, or bowel contents, depending on the clinical picture. Similar to thoracic pleural effusions, ascites fluid may be simple, complex, infectious, loculated, or debris filled. Again, a low-frequency curvilinear or phased-array transducer is generally used to interrogate for free fluid within the abdomen. With the patient supine, and with the transducer marker toward the head, the transducer is placed on the right and left flanks, approximately at the ninth/tenth intercostal space and angled in a slightly oblique angle to insonate between the rib spaces. This provides a view of the right and left hemi-abdominal potential spaces [28]. The final portion is the pelvic view, which is generally performed in both the transverse and sagittal planes, interrogating the retro-vesicular space in men and the rectovaginal space/pouch of Douglas in women [28]. The FAST exam has been reported to detect intraperitoneal fluid collections as small as 100 mL, with a median range of 250–620 mL commonly cited. The overall sensitivity and specificity of the FAST exam have been reported to be approximately 79% and 99%, respectively [42]. Similar to thoracentesis, ultrasound-guided paracentesis has been associated with a 68% decrease in bleeding complications when obtaining samples to better characterize the intra-abdominal fluid [35].

Immunocompromised oncologic patients are at increased risk for bowel perforation due to local infiltration, vascular

occlusion, or increased pressures from obstructive processes causing ischemia and necrosis of the intestinal wall [39]. Additionally, opportunistic infections such as cytomegalovirus, chemo-/radiotherapy, and steroids have been linked with spontaneous perforation [39]. In perforation, complex free fluid that is heterogeneous and echogenic may be visualized outside the luminal walls of the intestinal tract.

Colitis

Despite the benefits of new cancer treatments, many novel therapies including immune checkpoint inhibitors can lead to autoimmunity and immune-related adverse events resulting in significant morbidity [39]. Autoimmune processes, including graft-versus-host disease, and opportunistic gastrointestinal infections (e.g., cytomegalovirus or *Clostridium difficile*), can all lead to colitis. Neutropenic enterocolitis (NEC) is a common presentation of abdominal pain in oncologic patients, representing a spectrum of disease, which includes typhlitis, caused by inflammation of the gastrointestinal tract. Chemotherapy and neutropenia weaken the mucosal barrier allowing bacterial translocation across the intestinal wall, mucosal damage, intestinal hemorrhage, transmural necrosis, and local infiltration. NEC can mimic an acute surgical abdomen and is considered a diagnosis of exclusion. Ultrasound may help detect NEC by identifying bowel wall thickening (BWT). Clinically, the presence of BWT is associated with increased duration of symptoms and mortality [43]. Generally accepted criteria for diagnosis include BWT >4 mm (transverse scan) in any segment of the bowel for >3 cm in length (longitudinal scan) [44]. BWT >10 mm is associated with more severe disease and increased mortality [43]. The three mural layers of the gastrointestinal tract are often visualized as they become more edematous and generally have a distinct hyper-hypo-hyperechoic pattern [43]. Ultrasound imaging has also been found to be useful in monitoring the clinical response of patients with NEC by demonstrating measurable reductions in BWT. However, ultrasound does have some disadvantages compared to CT, including limited resolution in obese patients, operator dependency/training, lower sensitivity, and inability to completely evaluate or exclude other potential surgical causes of abdominal pain [44].

Genitourinary Oncologic Emergencies

Obstructive Urinary Pathologies

Patients with prostatic, vesicular, gynecologic, rectal, or intra-abdominal malignancies, metastases, or retroperitoneal lymphadenopathy/fibrosis are at risk for localized compression or obstruction of genitourinary structures which may, in turn, cause urinary retention, hydronephrosis, hematuria, anuria, and acute kidney injury or failure. The use of POCUS for the early identification of hydronephrosis or genitourinary lesions may guide management (e.g., radiation or decompression via nephrostomy, Foley catheter, or suprapubic aspiration) and help prevent these complications [39].

Similar to the abdominal evaluation as noted above, a low-frequency transducer is generally used for this view. With the patient supine, and with the transducer marker toward the head, the transducer is placed on the right and left flank approximately at the ninth/tenth intercostal space and angled in a slightly oblique angle to insonate between the rib spaces. The kidneys are identified on the right and left sides, caudal to the liver and spleen, respectively. To evaluate the bladder, place the transducer just superior to the pubic symphysis and aim the beam of the transducer inferiorly into the pelvis, scanning in two planes [28]. The presence of hydronephrosis is identified by a dilated collecting system at the center of the kidney, which is fluid filled and anechoic. Hydronephrosis is graded from mild to severe (Fig. 47.17). It is important to utilize the Doppler functionality to differentiate between a dilated collecting system and prominent renal vasculature, which normally produces a robust color Doppler signal.

Pelvic Pathologies

Patients with endometrial, ovarian, cervical, and metastatic cancer to the female pelvic organs may present to the emergency department with acute pelvic or abdominal pain. Adnexal masses greatly increase the risk of ovarian torsion, and POCUS may be useful in the initial screening.

The curvilinear, low-frequency transducer or endocavitary transducer is recommended for evaluating the pelvic organs. The endocavitary transducer provides better views and higher sensitivity in detecting subtle findings in early pregnancy and adnexal pathologies. B-mode is used for anatomic evaluation, and Doppler mode is necessary for assessing vascular supply and is particularly useful in cases of ovarian torsion. M-mode should be used to determine fetal heart rate as the use of Doppler carries a theoretical risk of thermal injury to a first trimester fetus and should be avoided.

Ovarian Torsion

Ovarian torsion is defined as an interruption to the ovarian vascular supply due to a rotation in the ovarian vascular ped-

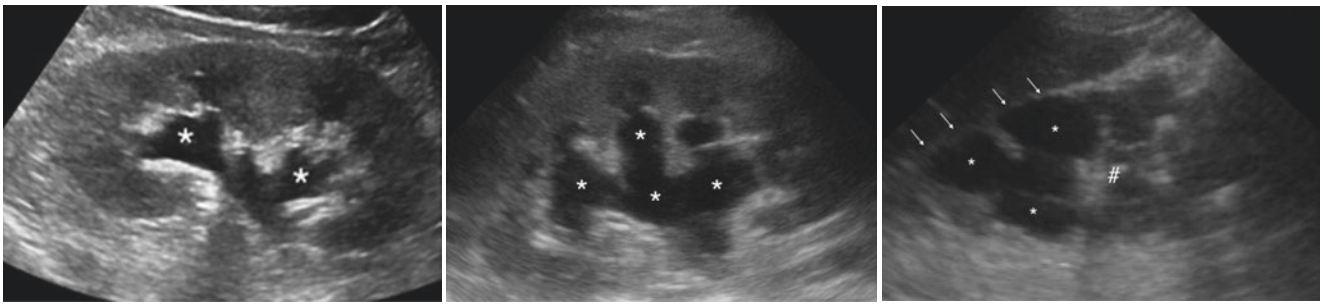

Fig. 47.17 Shown here is the spectrum of hydronephrosis including mild (*left*), moderate (*middle*), and severe (*right*). The presence of hydronephrosis (*) is identified by a dilated collecting system at the center of the kidney – it is fluid filled, and anechoic, and has absent color flow on color flow Doppler. Mild hydronephrosis has dilation of the renal pelvis only. Moderate hydronephrosis has dilation of both the renal pelvis and calyces. Severe hydronephrosis has ballooning of the renal pelvis and calyces with associated cortical thinning (*arrows*). In the image with severe hydronephrosis, there is an obstructing staghorn calculus (#)

icle which may result in ischemia and subsequent necrosis of the involved ovary [45]. Torsion begins with the twisting of the suspensory ligament which contains the ovarian artery, vein, and lymphatic vessel. Initially, the ovarian vein and lymphatic vessel are compromised which leads to ovarian edema. As the pressure increases within the ovarian capsule, arterial supply is ultimately compromised. Unfortunately, ovarian torsion is a difficult clinical entity to diagnose, as no one historical or exam feature or ultrasonographic finding can reliably exclude it [46]. As the number of sonographic signs suggestive of torsion increases, the likelihood of ovarian torsion increases [47].

Sonographic findings in ovarian torsion may include unilateral ovarian enlargement with diminished or absent Doppler flow. Other secondary signs include abnormal ovarian location, unilateral cyst or neoplasm, and free fluid in the pouch of Douglas.

The typical adult ovary measures 2 × 2 × 3 cm though in cases of unilateral edema it may be many times this size [8]. In ovarian torsion, stromal edema may also lead to displacement of visible follicles to the periphery of the ovary [47]. Color Doppler and spectral Doppler of the suspected ovary should be performed to confirm the presence of both arterial and venous flow. Absent Doppler flow greatly increases the likelihood of ovarian torsion, although the presence of flow does not rule out ovarian torsion [46]. Unilateral cysts or neoplasms may be visualized as anechoic or mixed-echogenicity lesions within the relatively homogenous hypoechoic echotexture of the ovary, although their presence or absence does not always predict or exclude torsion [46, 47].

Displacement of the ovary can sometimes be noted. For example, displacement of the ovary toward the midline and superior to the uterus, where it appears posterior to the bladder as another anechoic, fluid-filled structure, is known as the "double-bladder sign" [48]. Free fluid in the pelvis, either surrounding the affected ovary or in the pouch of Douglas, in combination with a suspicious exam, may also increase the likelihood of ovarian torsion [47].

Although POCUS is a feasible first-line modality in evaluating suspected cases of ovarian torsion, it may prove challenging to the inexperienced operator, and combination of this modality with CT, MRI, or radiology ultrasound, as well as early specialist consultation, should be considered.

Deep Venous Thrombosis

The hypercoagulable state of patients with malignancy makes them more susceptible to deep venous thrombosis (DVT). Only an estimated 50% of DVT cases present with the typical manifestations of unilateral upper or lower extremity edema, erythema, and pain [49]. In a study by Casella et al., the sensitivity of clinical examination in identifying bilateral DVT was 27.2%, and the estimated incidence of having bilateral DVT in patients presenting with unilateral signs was 32% [50]. Consequently, a high index of suspicion for DVT must be maintained.

With a sensitivity and specificity greater than 95%, the mainstay of bedside diagnosis of DVT is compression ultrasonography (CUS) [51]. CUS is considered the primary diagnostic test for those who have moderate to high pretest

probability based on the Wells score or physician gestalt. The combination of CUS plus D-dimer achieves a sensitivity of 100% for DVT [52]. The typical bedside CUS exam does not evaluate for a thrombus distal to the popliteal vein (PV). Therefore, in the setting of an initial negative bedside CUS but a positive D-dimer, a repeat CUS study 1 week later is recommended to evaluate for propagation of thrombus to the deep venous system at or proximal to the PV. However, if the initial D-dimer is negative, the diagnosis of DVT is ruled out and no additional CUS is needed [49].

The high-frequency linear transducer is used with the patient supine or in reverse Trendelenburg. The leg is externally rotated and abducted with the knee slightly flexed. The transducer is oriented transverse, inferior to the inguinal ligament with the indicator toward the patient's right. To exclude thrombus, compression with the ultrasound transducer should be applied until the lumen of the vein is completely flattened with the two walls touching each other (Fig. 47.18). If the lumen cannot be fully compressed, this is diagnostic of DVT. The common femoral vein (CFV) lies adjacent to the common femoral artery (CFA). Ideally, the transducer should initially be placed at the level where the greater saphenous vein (GSV) drains into the CFV. Although the GSV is considered superficial, a thrombus in the GSV has a higher probability of propagating into the CFV and becoming a DVT. Therefore, the GSV is evaluated for compressibility at the level of the CFV, as current guidelines recommend anticoagulation for thrombus within the proximal 5 cm of the GSV (Fig. 47.19). CUS is then performed distally in a continuous fashion by compressing at 1–2 cm intervals to the level of the adductor canal when the FV penetrates deeper and becomes difficult to assess [51]. To examine the popliteal vein (PV), the scan should be performed at the popliteal fossa with the knee slightly flexed. The vein is most often located superficial to or "on top of" the popliteal artery. Caution should be exercised as the popliteal vein is a relatively deep structure, and superficial vessels, depending on body habitus, may be mistaken for the PV.

Color and spectral Doppler may be used to help differentiate veins from other structures such as arteries, cysts, or lymph nodes, which may confuse inexperienced operators, such as in Fig. 47.19c.

US is not sufficiently sensitive in diagnosing more proximal VTE within the pelvic and abdominal veins. Additionally, an evaluation for VTE distal to the popliteal vein is not typically performed in bedside CUS exams as the sensitivity of CUS in diagnosing VTE in the calf is considered poor in symptomatic and asymptomatic VTE alike [49]. If the femoral and popliteal veins are not well visualized or their compressibility is questionable, additional diagnostic tests are needed, and the study should be deemed indeterminate due to insufficient data to make or exclude the diagnosis of DVT [52].

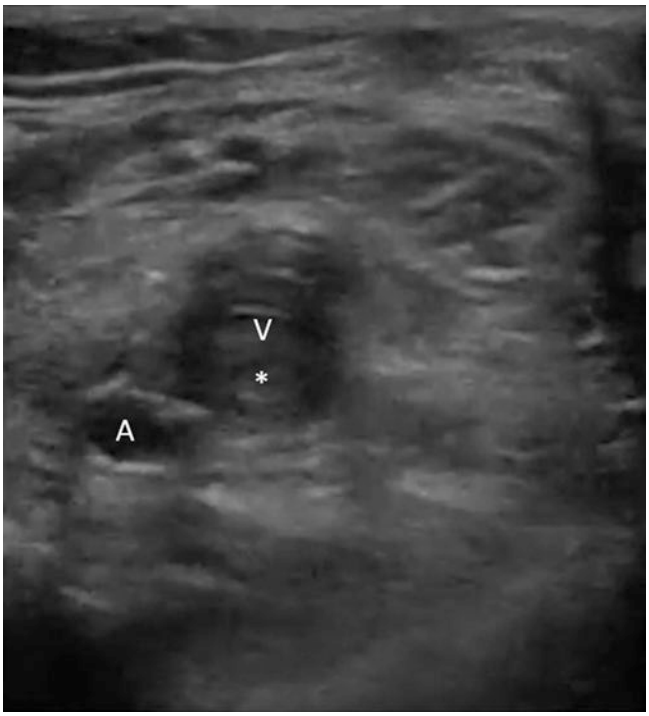

Fig. 47.18 The popliteal vein (V) seen here with an intramural thrombus (*) lies superficial to the artery (A) when examined at the popliteal fossa. The examiner is exerting pressure here to the extent that the artery is being partially compressed, but the vein (V) remains noncompressible which is consistent with DVT

Lymphadenopathy

Basic Approach

The linear transducer is used to image superficial lymph nodes. Color flow assessment adds critical information in the evaluation of lymph nodes.

Superficial Lymph Nodes: Benign Versus Malignant

POCUS can be used to evaluate superficial lymph nodes. Features such as size, shape, presence or absence of the hilum,

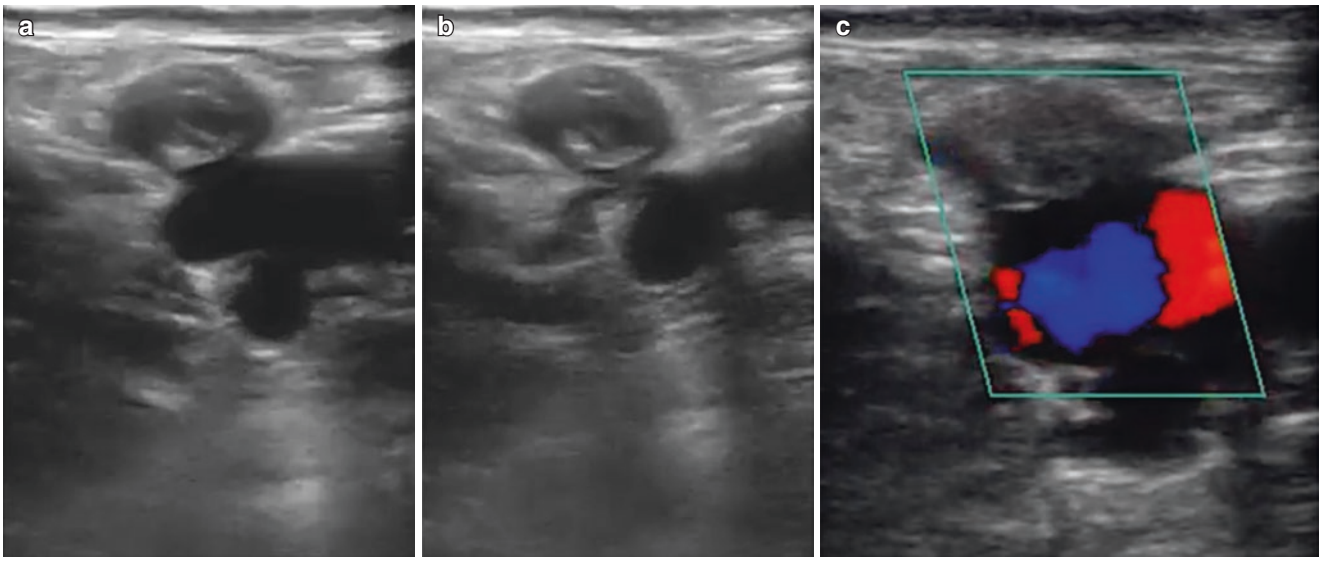

Fig. 47.19 A DVT involving the greater saphenous vein (GSV) at the junction with the common femoral vein (CFV). (**a**) An echogenic thrombus is seen in the lumen of the GSV with a patent anechoic CFV inferomedial to it. (**b**) With compression, the GSV does not compress, whereas the lumen of the CFV is completely obliterated with compression indicating the presence of a DVT in the GSV but not the CFV. (**c**) Applying color Doppler shows the presence of flow within the lumen of the CFV but not the GSV where the thrombus is present

echogenicity, margins, and structural changes may be useful in distinguishing benign from malignant lymph nodes [53]. Color flow evaluation of the presence, location, and pattern of flow within the lymph node aids in this differentiation.

Size and Shape

Size and shape are lymph node characteristics reflected in the ratio between the longitudinal and the transverse or short-axis nodal measurement, termed an L/S ratio. In general, benign lymph nodes are oval, and their longitudinal axis is at least twice the transverse/short-axis measurement. Malignant lymph nodes are more often round and their L/S ratio is less than 2 [53].

Hilar Appearance

Typically, benign nodes have a central, echogenic hilum, whereas malignant lymph nodes are more likely to have absence of the hilum.

Margins

Benign nodes will have a sharp, well-defined margin, while malignant nodes may demonstrate irregular, angular, or blurred margins.

Structural Characteristics

Structural changes such as intranodal necrosis, calcification, and matting are all suggestive of malignancy. Intranodal necrosis that appears as an anechoic area of fluid within the lymph node may indicate malignancy but can also be seen in intranodal abscess or tuberculosis. Intranodal calcifications may be seen in thyroid malignancies but are rarely seen in other malignancies. Matting of lymph nodes where multiple nodes are fused in a single, poorly defined mass is seen in malignancy when there is extracapsular invasion and in infections such as tuberculosis and mononucleosis. Matting is not typically seen in reactive lymph nodes and is, therefore, useful in differentiating malignant from reactive lymph nodes. Peripheral halo and perinodal edema may be seen in tuberculosis or malignancy but are not encountered in reactive nodes [53].

Color Flow

In benign lymph nodes, a single central, vascular pedicle entering the hilum may be visualized with color flow. In contrast, malignant lymph nodes may demonstrate multiple vascular pedicles, mixed peripheral and central color flow, or overall increased color flow due to increased vascularization.

POCUS Use in Pediatric Neck Masses

In one retrospective study of children presenting with neck masses to an ED, POCUS performed by pediatric EM physicians showed 100% agreement with final diagnosis by radiology department imaging for the category of "lymph node with malignant features" [54]. All four children whose neck mass was concerning for malignant lymphadenopathy subsequently received the diagnosis of Hodgkin lymphoma. If US evaluation of the neck mass revealed a lymph node with altered architecture, loss of the central hilum, a heterogeneous echo texture, and an abnormal blood supply, it was categorized as a "lymph node with malignant features."

A case series also demonstrated that POCUS evaluation of pediatric neck swelling can identify lymphadenopathy and further characterize the lymphadenopathy as reactive lymphadenitis, abscess collection secondary to suppurative lymphadenitis, disseminated tuberculosis, and concerning for malignancy (first case with lymphadenopathy with hyperechoic foci due to calcifications, second case with enlarged lymph nodes with loss of normal echotexture and destruction of the outer capsule) [55].

A prospective pilot study involving a convenience sample of pediatric patients also suggests that pediatric EM physicians are able to use POCUS to effectively evaluate undifferentiated soft tissue neck masses in the ED. POCUS was found to be 78% accurate in the sonographic assessment of soft tissue neck masses when compared to radiology department imaging and most often diagnosed infectious or inflammatory conditions [56].

Rapid Ultrasound in Shock and Hypotension (RUSH)

Case Study

A 55-year-old female with history of metastatic breast cancer presents with altered mental status. She last received her chemotherapy via *her port 5 days ago and has been ill for 1 day. Her partner reports that she awoke this morning confused and lethargic but is unable to provide further history.*

The patient is ill-appearing, pale, and diaphoretic on exam. Vital signs are as follows: temperature 99.2 °F, pulse 132, SpO2 96% on room air, respiratory rate 24, and blood pressure 86/50. Her right-sided chest port is palpable. Decreased breath sounds are noted bilaterally, and tachypnea is present without accessory muscle use. Heart rate is regular and there are no murmurs heard. Abdomen is mildly distended but non-tender to exam. No extremity edema is noted.

A RUSH protocol was initiated. On evaluation of the "pump," a large pericardial effusion was noted as well as diastolic compression of the right ventricle. The "tank" evaluation demonstrated a large IVC with minimal respiratory change. Suspecting tamponade physiology, the ED team performed an ultrasound-guided pericardiocentesis, with marked improvement in the patient's blood pressure and mental status.

The RUSH protocol is one of several systematic approaches to the undifferentiated hypotensive and hypoperfused medical patient. It allows the rapid identification of several pathologies which frequently afflict oncologic patients, including cardiac tamponade, septic shock, intra-abdominal hemorrhage, massive pulmonary embolism, and acute decompensated heart failure (Fig. 47.20) [3–5]. The RUSH exam integrates multiple applications as discussed above, including cardiac, thoracic, abdominal, and vascular ultrasound.

HI MAP ED Approach

The RUSH exam uses a phased-array or curvilinear transducer, and its components are captured in the "HI MAP ED" mnemonic (heart, IVC, Morison's pouch, aorta, pulmonary, ectopic, DVT). The *heart* is the first organ assessed in the RUSH exam using a phased-array transducer (or curvilinear transducer if this is not available), obtaining at least two of the four cardiac views, generally starting with the parasternal views. The heart is evaluated for the presence of pericardial effusion and, if one is present, whether there is associated tamponade (see Fig. 47.20). The LV ejection fraction is estimated or can be measured through M-mode measurement of EPSS. The right heart is assessed for signs of RV strain, including RV dilation, McConnell's sign, septal wall flattening, or decreased TAPSE, all of which raise suspicion for pulmonary embolism.

Next, the *IVC* is evaluated in the subcostal window. The presence of IVC dilation or decreased CI concurrent with pericardial effusion raises suspicion for tamponade, while its coexistence with right heart strain increases suspicion for acute obstructive shock.

The next areas to be evaluated are *Morison's* pouch in the right upper quadrant and the splenorenal space in the left upper quadrant. In oncologic patients, the frequent occurrence of ascites complicates this portion of the exam, as

ultrasound is insufficient to delineate the nature of the fluid in the abdominal cavity and cannot determine if it represents simple ascites or hemoperitoneum.

The next window of the RUSH exam is the *aortic* slide view, where the aorta is visualized in the transverse axis and assessed for evidence of aneurysm, defined as an anteroposterior diameter greater than 3 cm [57].

The *pulmonary* views are then evaluated, using the technique as described above, assessing the lungs for the presence or absence of the following pathologies: pneumothorax, pleural effusion, and B-lines or diffuse interstitial syndrome.

In female patients of child-bearing age, a pregnancy test should be checked, and the pelvic view examined for evidence of *ectopic* pregnancy. The presence of a positive pregnancy test plus free fluid in the right upper quadrant, especially in a patient without known ascites, increases the likelihood of the need for operative intervention [58, 59]. The uterus should be examined for the presence or absence of intrauterine pregnancy, which at a minimum requires the presence of a yolk sac or a fetal pole within a fluid-filled gestational sac in the uterus [8].

The presence or absence of *DVT* should be assessed with compression ultrasound of the bilateral legs. The finding of DVT plus evidence of right heart strain in a hypotensive patient may be considered diagnostic of a massive pulmonary embolus, and institutional protocols should be followed to consider the administration of thrombolytics, activation of interventional radiology, or activation of a specialized PE response team.

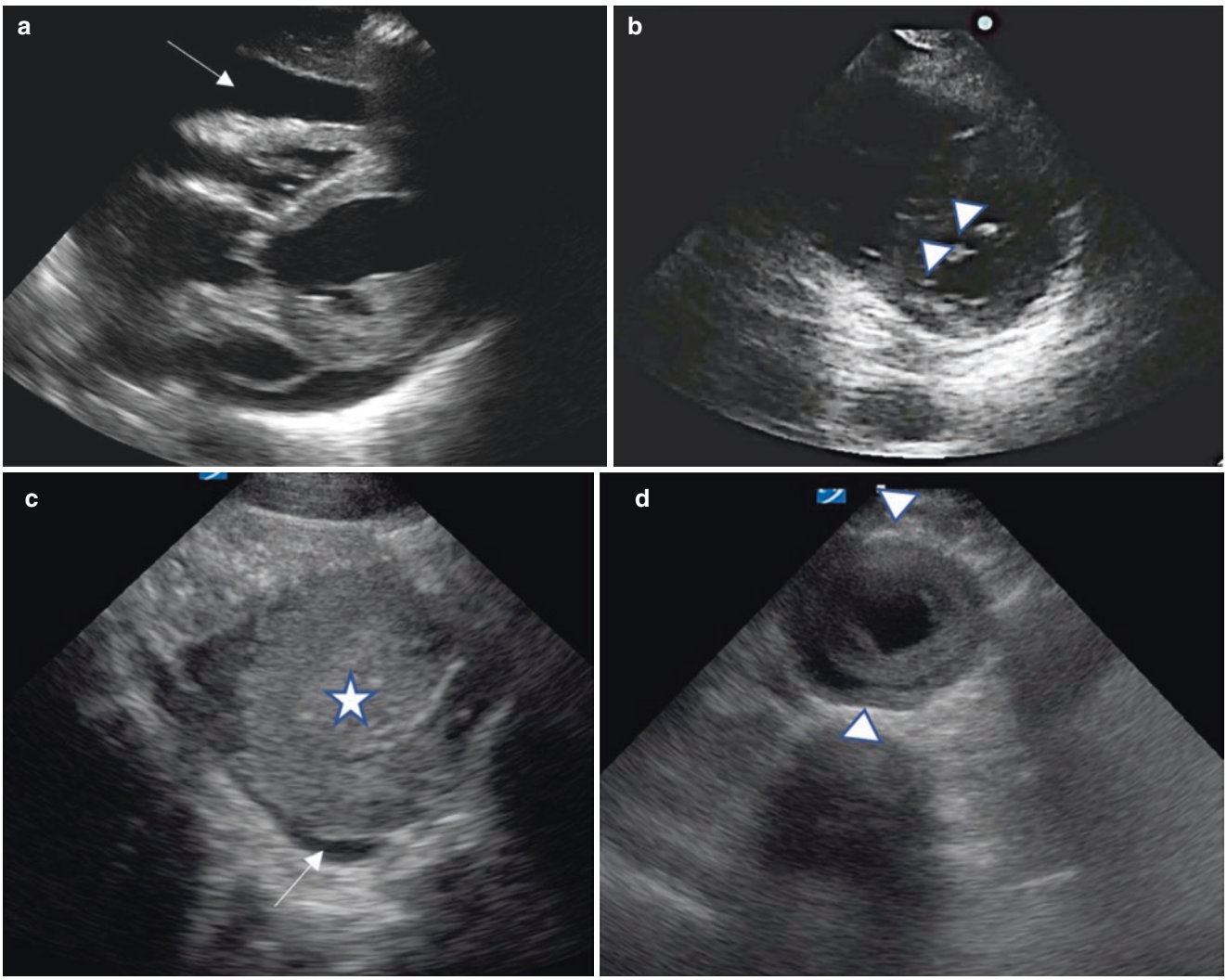

Fig. 47.20 Examples of pathological findings identified using the RUSH protocol. (**a**) Pericardial effusion seen on the subxiphoid view (*arrow*). (**b**) Interventricular septal deviation toward the, known as the D sign for the D shape of the LV. A sign of elevated RV pressure as may be seen in PE (*arrowheads*). (**c**) Minimal free fluid in the pelvic area (*arrow*) seen posterior to the uterus (*). (**d**) Abdominal aortic aneurysm (*arrowhead*) measuring 6 cm in diameter (<3 cm is normal). (**e**) Significant IVC respiratory variation with nearly complete IVC collapse as may be seen in hypovolemia (*arrows*). (**f**) Multiple B-lines extending from the pleura to a depth of 18 cm concerning for diffuse interstitial syndrome. (**g**) A significant pleural effusion (*) superior to the diaphragm and liver (L)

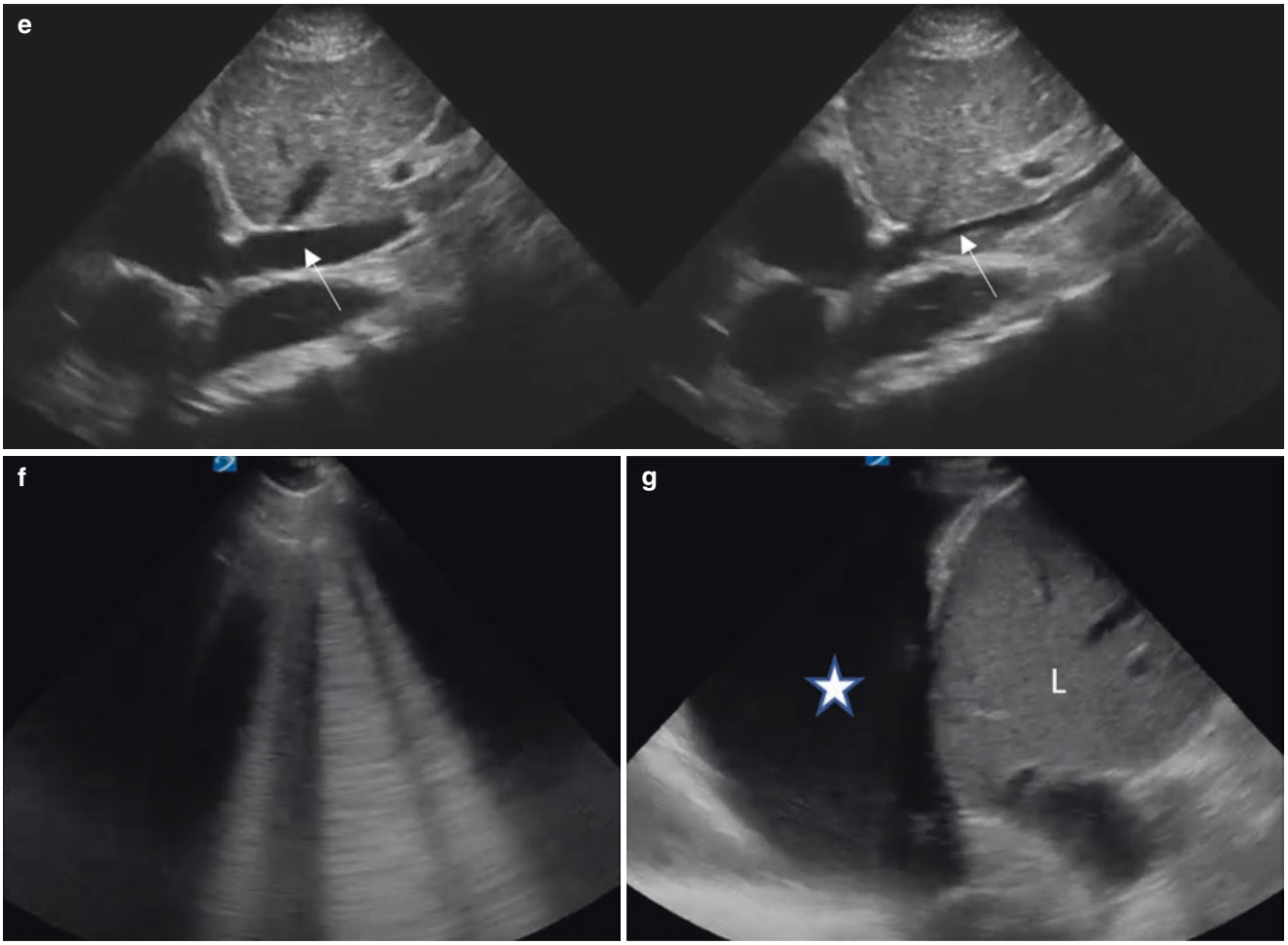

Fig. 47.20 (continued)

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Part IV

Toxicities

Chemotherapy Toxicities

48

Katy M. Toale, Tami N. Johnson, Maggie Q. Ma, and Ngoc H. Vu

Introduction

There are many agents available to treat cancer. Chemotherapy, which includes but is not limited to alkylating agents, nitrosoureas, antimetabolites, antitumor antibiotics, topoisomerase inhibitors, and mitotic inhibitors, fights cancer through targeting cancer cells at different cell cycle phases. Other types of therapies used to treat cancer include targeted therapies, hormone therapy, and immunotherapy. Chemotherapy toxicity is a common and unfortunate consequence of therapy that can occur even at usual doses. Often these toxicities warrant emergency care. Timely recognition and appropriate management of chemotherapy toxicity in the emergency department (ED) is imperative.

While this chapter will not address all chemotherapy toxicities, we will discuss the most frequently encountered issues in the ED. Certain toxicities such as diarrhea, tumor lysis syndrome, myelosuppression, neutropenic fever, and mucositis are discussed in other chapters.

This chapter will include a review of the following chemotherapy toxicities: central nervous system toxicity, peripheral neuropathy, hypertensive crisis, nausea and vomiting, nephrotoxicity, electrolyte disorders, anaphylaxis, and extravasation.

It is important for clinicians working in the emergency setting to understand these chemotherapy toxicities and know how to manage them. Patient and caregiver education is also crucial because many of these serious side effects can occur while the patient is not hospitalized.

Case Study

BA is a 55-year-old male with bladder cancer being treated with cisplatin as part of his chemotherapy regimen. He presents to your ED complaining of weakness, fatigue, tinnitus, and paresthesias in his fingers and toes. He is able to answer questions, but his family states he has been having increasing confusion since yesterday. He has been experiencing severe nausea and vomiting and has been unable to keep any food or liquid down in the past 3 days. He is also unable to take his antiemetic medications. His vital signs are 84/65 with a heart rate of 120. His laboratory values are significant for a magnesium level of 1.1 mEq/L and sodium of 120 mEq/L and a serum creatinine of 3.5 mg/dL (baseline is 1.2 mg/dL). A computed tomography (CT) scan of the brain is unremarkable. Cisplatin is an alkylating agent with many toxicities. One of the major dose-related toxicities is nausea and vomiting which BA has been experiencing. This has caused severe dehydration and electrolyte abnormalities. In addition to nausea and vomiting, cisplatin can also cause nephrotoxicity, which manifests as hypomagnesemia and syndrome of inappropriate antidiuretic hormone (SIADH), causing hyponatremia. The tinnitus may be related to the ototoxicity of cisplatin, and the paresthesias could be related to the peripheral neuropathy associated with this chemotherapy agent. Management in the ED would include IV hydration, antiemetics, and electrolyte replacement, as well as initiation of an agent to improve the symptoms of neuropathy.

Central Nervous System (CNS) Toxicities

Chemotherapy drugs that readily cross the blood–brain barrier or administered via the intrathecal or intraventricular route can cause neurotoxicity [1]. CNS toxicity encompasses many different syndromes such as headache, somnolence, confusion, seizures, aseptic meningitis, cerebellar dysfunction, encephalopathy, intracranial hemorrhage, stroke, myelopathy, hearing loss, blindness, dementia, and coma.

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Table 48.1 Central nervous system toxicities and associated chemotherapy agents [1–3]

CNS toxicity	Agent	
Intracranial hemorrhage	Antiangiogenic agents[a]	Asparaginase
Encephalopathy	Asparaginase Busulfan Carmustine Cisplatin Cytarabine Fluorouracil Ifosfamide	Lomustine Melphalan Methotrexate Paclitaxel Procarbazine Vincristine
Posterior reversible encephalopathy syndrome (PRES)	Antiangiogenic agents[a] Cisplatin Cytarabine Capecitabine	Gemcitabine Ifosfamide Fluorouracil Vincristine
Seizures	Busulfan Carmustine Cisplatin Cytarabine Fluorouracil Oxaliplatin	Ifosfamide Lomustine Methotrexate Paclitaxel Vincristine Any intrathecal chemotherapy agent
Cerebellar syndrome	Cytarabine	Fluorouracil
Stroke	Antiangiogenic agents[a] Cisplatin	Methotrexate
Aseptic meningitis	Cytarabine Thiotepa Topotecan	Methotrexate Any intrathecal chemotherapy agent
Myelopathy	Cytarabine	Methotrexate
Ototoxicity	Carboplatin	Cisplatin
Blindness	Carboplatin Cytarabine	Lomustine Vincristine
Dementia	Methotrexate	

[a]Antiangiogenic agents include bevacizumab, sorafenib, and sunitinib

Risk factors for developing CNS toxicity depend on the chemotherapy but may include high dosages, intrathecal or intraventricular administration, frequent administration, renal dysfunction, and hepatic dysfunction [2]. This section will focus on the more common acute neurotoxicities and their associated chemotherapy; a more extensive list of neurotoxicities caused by chemotherapy can be found in Table 48.1 [1–3].

Chemotherapy Agents Implicated

Methotrexate

Methotrexate does not easily cross the blood–brain barrier. Neurotoxicity is associated with intrathecal administration or high doses of intravenous methotrexate (>500 mg/m^2) [4]. Toxicity may be due to folate or homocysteine imbalance or direct neuronal injury [5, 6]. Neurotoxicity can present in many different forms. Intrathecal methotrexate causes aseptic meningitis in greater than 10% of patients [7]. Patients typically experience headache, nausea, vomiting, nuchal rigidity, and fever. This can occur 2–4 h after methotrexate administration and last up to 12–72 h. Although this toxicity is generally self-limiting, corticosteroids such as dexamethasone can be given to prevent or treat methotrexate-induced aseptic meningitis [7].

Methotrexate neurotoxicity can also present at different times. Acute reactions occur as soon as hours after drug administration and can include aseptic meningitis as mentioned above, somnolence, seizures, stroke-like symptoms, or mental status changes [8]. Subacute neurotoxicity may present as confusion, ataxia, hemiparesis, and seizures, generally occurring 5–10 days after therapy [2]. Subacute neurotoxicity typically resolves without intervention. Lastly, chronic or delayed neurotoxicity can present months to years later, with dementia, personality changes, leukoencephalopathy, gait disturbances, aphasia, coma, and death [2, 7, 8]. These toxicities may be related to concurrent or past radiation, concomitant chemotherapy, or larger cumulative doses greater than 140 mg via the intrathecal route [2, 8]. Radiation may cause vascular injury and alter the blood–brain barrier, allowing higher methotrexate concentrations to reach the CNS [9].

MRI imaging findings include white matter damage, diffuse white matter hyperintensity, ventricular enlargement, cortical calcifications, or cerebral atrophy [2, 8]. Leucovorin rescue therapy is usually given 24 h after methotrexate dose to decrease the toxicity associated with methotrexate folate imbalance [7]. Leucovorin 15 mg (~10–15 mg/m^2) is given every 6 h for approximately 72 h, and levels may vary based on renal function and methotrexate elimination [4].

Cytarabine

Cytarabine can be given via intravenous or intrathecal administration. It is known to cross the blood–brain barrier at high intravenous doses. The primary neurotoxicity caused by cytarabine is cerebellar dysfunction (dysarthria, ataxia, nystagmus), occurring in 10–20% of patients at doses greater than 27–36 g/m^2, and occasionally with encephalopathy and seizures [2, 7, 8]. Cytarabine is metabolized primarily by the liver and excreted in the urine. Hepatic or renal dysfunction can lead to decreased clearance and accumulation of cytarabine [10]. Neurotoxicity is commonly seen with higher doses, in elderly patients, or in patients with renal or hepatic dysfunction [8]. The onset is generally 3–8 days after drug administration and usually resolves upon drug discontinuation but can last for weeks or months. Cytarabine also can cause loss of Purkinje cells and permanent impairment [8, 11]. MRI imaging will depict cerebellar atrophy and reversible white matter changes [2]. Other CNS toxicities that can be seen with cytarabine include blurred vision, burning eye pain, blindness, confusion, somnolence, and myelopathy [2]. Although rare, intrathe-

cal cytarabine can cause aseptic meningitis, thought due to an immunologic response [1]. Steroid prophylaxis may prevent recurrence [10].

Ifosfamide

Up to 10–30% of patients receiving ifosfamide can experience some form of neurotoxicity, generally in the form of encephalopathy. Confusion is the most prevalent symptom, occurring in up to 80% of patients. Hallucination and psychosis can occur in up to 30% of patients, and other neurotoxicities such as lethargy, personality changes, extrapyramidal symptoms, hallucinations, seizures (including nonconvulsive seizures), and dysarthria are less common and can begin within 24 h of drug administration [2]. These toxicities are usually reversible within a few days of drug discontinuation, but cases of coma and death have occurred [12].

Risk factors for ifosfamide neurotoxicity include high doses, low albumin (potentially related to hepatic dysfunction), renal dysfunction, tumor in the lower abdomen/pelvis, pretreatment with cisplatin, oral administration, shorter intravenous (IV) infusion time, and prior CNS disease [7, 12, 13]. It is postulated that ifosfamide neurotoxicity is due to the ifosfamide metabolite, chloroacetaldehyde. Chloroacetaldehyde crosses the blood–brain barrier and can cause direct neurotoxic effects [12, 13]. Chloroacetaldehyde also depletes glutathione stores that are needed to protect against toxicity [14].

Brain imaging for ifosfamide neurotoxicity usually shows no abnormalities, and diagnosis is generally based on exclusion of other causes [12]. Although symptoms usually resolve spontaneously, methylene blue has been reported to shorten recovery time and prevent recurrence [12, 13, 15]. An electroencephalogram should be performed in patients presenting with altered mental status to rule out nonconvulsive seizures. Patients with seizures should be treated with a benzodiazepine.

Busulfan

Busulfan readily crosses the blood–brain barrier and is commonly used in high doses in conditioning regimens for patients undergoing hematopoietic stem cell transplantation [16]. The most common neurotoxicity in patients receiving high-dose busulfan is seizures, oftentimes warranting seizure prophylaxis prior to administration of busulfan. The incidence of seizures in patients who do not receive seizure prophylaxis ranges from 5% to 15% [7]. Risk factors for seizures include older age and higher doses of 600 mg/mg^2 or 16 mg/kg [17, 18]. Seizure onset typically occurs within hours of busulfan administration but may occur up to 24 h after the dose is complete [7, 16]. Busulfan-induced toxicity generally presents as tonic–clonic seizures, but electroencephalography (EEG) abnormalities can be present without apparent seizures. Historically, phenytoin has been used as seizure prophylaxis in patients receiving busulfan, but caution is warranted with this agent due to its effect on busulfan metabolism. Other agents that have been recommended include levetiracetam in combination with benzodiazepines [16].

Platinum-Based Compounds (Cisplatin, Carboplatin, Oxaliplatin)

The most common form of central neurotoxicity seen with platinum-based compounds is ototoxicity (presenting as tinnitus and hearing loss), occurring in up to 20–40% of patients [19]. Ototoxicity is more common with cisplatin compared to carboplatin and oxaliplatin. Platinum-based compounds accumulate in auditory sensory cells and lead to permanent hearing loss [20]. Ototoxicity is potentially related to high cumulative dose >400 mg/m^2, older age, renal dysfunction, and a longer duration of therapy [21, 22]. Other forms of CNS toxicity are rare. Cisplatin administration can cause direct neurovascular toxicity manifesting as encephalopathy, cortical blindness, stroke, seizures, and focal deficits [2, 20, 23]. Concomitant use of cisplatin with other chemotherapy agents or electrolyte abnormalities can increase the risk of neurotoxicity [1, 24].

Diagnosis and Treatment

Chemotherapy-induced neurotoxicity is a diagnosis of exclusion. Other causes for neurologic changes should be ruled out and treated. The treatment of chemotherapy-induced neurotoxicity generally involves prompt discontinuation of the offending agent. Depending on the agent, rechallenge with dose reductions and/or longer intervals between cycles may be considered [2]. In many cases, neurotoxicity is reversible upon discontinuation though it may take months for recovery; however, it can be irreversible and lead to permanent CNS damage.

Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) can significantly worsen quality of life and have an effect on cancer treatment due to dose reductions, treatment delays, and/or discontinuations [25]. In addition, this toxicity can also result in excessive healthcare costs and resources utilized [26]. Certain factors place patients at higher risk for nerve damage. These include the type of chemotherapy used, duration of treatment, cumulative dose, age, diabetes, African race, folate/vitamin B12 deficiency, smoking, impaired renal function, cancer-associated neuropathy, and prior or concomitant use of neurotoxic agents [25, 27].

Pathophysiology

The exact cause of CIPN differs between classes of chemotherapy agents. For platinum-based chemotherapy, it is thought the antitumor mechanism causes changes in the function of neuronal and glial cells. Mitochondria dysfunction can result in neuroinflammation, DNA damage, and axonal degeneration. Mechanisms for taxane-induced CIPN include axonal microtubule disruption, mitochondrial dysfunction, axon degeneration, altered calcium homeostasis, changes in peripheral nerve excitability, and activation of the immune system with development of neuroinflammation. Vinca alkaloids cause changes to large axons and dorsal root ganglion (DRG) neurons, leading to hyperexcitability of peripheral neurons and activation of immune cells, which leads to neuroinflammation. Bortezomib causes mitochondrial damage, increases in sphingolipid metabolism within astrocytes, and activation of immune cells, which results in neuroinflammation. Potential mechanisms for thalidomide-induced CIPN include an antiangiogenic effect, which may cause damage to sensory neurons and downregulation of tumor necrosis factor alpha (TNF-α) levels and inhibition of nuclear factor kappa B (NF-κB), which accelerates neuronal cell death. Ixabepilone-induced CIPN is postulated to cause microtubule disruption, damage of mitochondria, and activation of immune cells, resulting in neuroinflammation [27].

Epidemiology

Estimates vary but according to a recent review, 68% of patients develop CIPN after the first month of therapy, 60% at 3 months and 30% after 6 months [28]. There are many assessment methods for CIPN, but no single method is considered superior. This leads to a wide range in the reported prevalence of CIPN [29]. A detailed list of the most common agents implicated, incidence, and risk factors can be seen in Table 48.2 [25, 27, 30].

Presentation/Diagnosis

Peripheral neuropathy is clinically defined as any form of damage, inflammation, or degeneration of peripheral nerves. Patients may experience sensory nerve damage in addition to motor and autonomic nervous system damage. Symptoms usually present within the first 2 months of chemotherapy treatment and can progress until treatment is discontinued [27, 30]:

- Most often, symptoms are sensory, including paresthesias and pain.
- Symptoms may occur at any time during treatment, even after treatment is stopped.
- Symptoms are most often symmetrical.

Table 48.2 Characteristics of chemotherapy agents that cause chemotherapy-induced peripheral neuropathy [25, 27, 30]

Chemotherapy agent	Incidence	Additional risk factors	Others
Taxanes Paclitaxel Docetaxel	11–87% More common Less common	Cumulative dose Duration of infusion Simultaneous administration of platinum-based compounds History of peripheral neuropathy	Symptoms include paresthesia, numbness, or neuropathic pain in the hands and feet Symptoms usually improve after discontinuation but can continue indefinitely
Platinum-based compounds Cisplatin Oxaliplatin	70–100%	Cumulative dose Longer exposure times Oxaliplatin only: Cold temperatures Time of infusion Low body weight Preexisting peripheral neuropathy	Symptoms include numbness, tingling, and paresthesia in the hands and feet Symptoms usually improve or resolve within a year of completion of therapy; however, in some cases, the damage is not reversible "Coasting" phenomenon possible with worsening symptoms following discontinuation
Vincristine	60%	Cumulative dose	Symptoms include pain in hands and feet, muscle weakness, and cramping Symptoms are reversible upon discontinuation of therapy
Bortezomib	34%	Higher dosages Less toxicity with subcutaneous administration	Symptoms include chronic sensory peripheral neuropathy often with a neuropathic pain syndrome Occurs early in treatment and may last for weeks, months, or even years after discontinuation
Thalidomide	20–60%	Cumulative dose Advanced age Prior neuropathy	Symptoms include paresthesias, numbness and loss of dexterity on the toes and fingers
Ixabepilone	60–65%	Cumulative dose Prior doses of chemotherapy	Symptoms include paresthesia, numbness, or neuropathic pain in the hands and feet Symptoms usually improve after discontinuation

- Symptoms begin in the fingers and toes and spread proximally.
- In severe cases, loss of sensory perception can occur.

Prevention

Unfortunately, no agents have been proven beneficial for the prevention of CIPN [30]. Venlafaxine demonstrates some benefit for prevention of oxaliplatin CIPN; however, it is not routinely used due to concerns regarding its anticancer activity [31]. The clinician can consider dose reduction or discontinuation of the offending agent for patients unable to tolerate CIPN symptoms [25].

Management

Several agents have been tested for efficacy in treating CIPN. The most commonly used treatments for CIPN include topical amitriptyline/ketamine/baclofen, gabapentin, pregabalin, and duloxetine. Tricyclic antidepressants are commonly used in other neuropathic pain syndromes but have shown no benefit for CIPN, and adverse effects are a limitation. Characteristics of each medication can be seen in Table 48.3 [32]. Unfortunately, there is no gold standard for CIPN detection and grading, making clinical trials difficult to compare. Recently, guidelines on designing trials for prevention of CIPN have been published [33].

The agent with the highest level of recommendation for treatment of CIPN is duloxetine. Initial pilot studies utilizing duloxetine showed promise [34, 35]. Duloxetine was then evaluated in a randomized, double-blind, placebo-controlled crossover trial of 231 patients with CIPN from paclitaxel or oxaliplatin. Patients in the duloxetine group experienced less pain as well as a greater decrease in the pain that interfered with daily functions. The patients with oxaliplatin-induced peripheral neuropathy had better outcomes than patients on a taxane, and this may be explained by the different mechanisms causing CIPN [36]. Another ongoing trial should provide additional information to guide duloxetine use in CIPN [37].

In a study evaluating topical baclofen 10 mg, amitriptyline 40 mg, and ketamine 20 mg in pluronic lecithin organogel vs. placebo for CIPN, the topical compound showed a trend toward improved outcomes with no toxicities reported [38].

Gabapentin and pregabalin are used frequently for many types of neuropathic pain; however, current data does not support their use in CIPN. A trial of 115 patients who were randomly assigned to gabapentin or placebo showed no difference in outcomes [39]. Pregabalin was shown to improve outcomes in smaller trials [40]; however, a phase 4 study was terminated early when an interim analysis failed to detect a difference in outcomes [41].

Acupuncture has been studied for CIPN, and at this time there is not enough evidence to recommend it; however, it is considered safe and could potentially benefit patients suffering from CIPN [42]. Occupational and physical therapy trials are also limited but offer potential benefits to issues commonly faced by patients with CIPN, including gait issues, impaired postural control, and altered sensory organization [43].

Table 48.3 Characteristics of agents used in the treatment of chemotherapy-induced peripheral neuropathy (CIPN) [32]

Agent	Dose	MOA	Adverse effects	Comments
Duloxetine	30 mg PO daily for 1 week and then increase to 60 mg PO daily	Potent inhibitor of neuronal serotonin and norepinephrine reuptake and a weak inhibitor of dopamine reuptake	Fatigue Insomnia	Best evidence to support use in CIPN
Pregabalin	150 mg daily initially and then increase to 300–600 mg in two divided doses	Modulates calcium channel activity by binding to the α2δ receptor site	Somnolence Dizziness Peripheral edema Xerostomia Ataxia Weight gain	Schedule V controlled substance Do not discontinue abruptly
Gabapentin	300–900 mg daily initially and then increase to 1200–3600 mg in three divided doses	Modulates calcium channel activity by binding to the α2δ receptor site	Somnolence Dizziness Ataxia Confusion Disorientation	Do not discontinue abruptly
Topical amitriptyline/ketamine/baclofen	Apply two to three times daily	Amitriptyline: increases the synaptic concentration of serotonin and/or norepinephrine in the CNS by inhibition of their reuptake Ketamine: noncompetitive NMDA receptor antagonist that blocks glutamate	Anticholinergic effects Postural hypotension Sedation	Formulations vary and can include other agents such as lidocaine

CNS central nervous system, *MOA* mechanism of action, *NMDA* N-methyl-D-aspartate receptor, *PO* by mouth

Hypertensive Crisis

Hypertension is common in the general population and can lead to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately [44]. Hypertension is a known long-term comorbidity of many patients with malignancy. The prevalence before treatment is similar to the community but increases after the initiation of chemotherapy and targeted agents [45]. The incidence of hypertension depends on age, cardiovascular comorbidities, type of malignancy, treatment regimen, and concomitant medications [46]. The estimated risk in patients with malignancy is as high as 36% [47].

Pathophysiology

The mechanisms underlying worsening hypertension in patients with malignancy are not well understood. It is hypothesized that certain chemotherapy and targeted or supportive agents associated with hypertension contribute to endothelial dysfunction with nitric oxide reduction, increase in vascular tone, decrease density of microvessels, renal thrombotic microangiopathy that leads to proteinuria, arterial vasoconstriction, sodium and fluid retention, and activation of the renin–angiotensin system [46].

Clinical Features

As in the general population, patients with malignancy are at risk for hypertensive crisis. For all levels of hypertension severity, including crisis level, Fraeman and colleagues reported that the incidence was considerably higher during periods of chemotherapy exposure versus without exposure. Patients experiencing crisis-level hypertension rates during exposure versus without, respectively, were 8.98 and 2.09 cases per 100 person-years [47]. Hypertensive emergencies are always associated with end-organ damage, such as hypertensive encephalopathy, cerebral infarction or hemorrhage, myocardial ischemia or infarction, heart failure, aortic dissection, and/or renal failure. Hypertensive emergency is not related to any specific blood pressure (BP) number but usually involves an acute elevation of the systolic BP (SBP) greater than 180 mm Hg or diastolic BP (DBP) above 120 mm Hg. The pace of the rise and percent increase in BP as well as the presence of end-organ damage is far more important than the actual number and demands immediate interventions to prevent further end-organ damage [48, 49].

Chemotherapy and Targeted Agents Implicated

The higher rate of hypertension in patients with malignancy can be contributed to the use of chemotherapy and targeted agents that can cause hypertension (angiogenesis inhibitors, 17–80%; alkylating agents, 36–39%; and immunosuppressants after stem cell transplantation, 30–80%) [45, 46]. Disruption of vascular endothelial growth factor (VEGF) signaling using antibody against VEGF-A (bevacizumab), antibody against receptor for VEGF (VEGFR2) (ramucirumab), and small molecule inhibitors of receptors for VEGF (sunitinib, sorafenib, etc.) is associated with hypertension, and its occurrence may be a useful marker of efficacy for these agents [50]. Some of the end-organ effects (e.g., heart failure, stroke, or renal failure) of these chemotherapy agents can compound hypertension or cause primary hypertensive crisis. Over 150 chemotherapy and targeted agents have been associated with hypertension, heart failure, stroke, and/or renal failure [32, 46].

Treatment

There is no specific guideline for treating hypertension or specifying which agents to use in patients with malignancy. Patients with hypertensive urgency should be treated, and this is usually achieved by administering oral agents followed by several hours of clinical observation [49, 51] (see Table 48.4 [32, 48, 52]).

Aggressive blood pressure control is mandatory for patients with hypertensive emergency in order to minimize the risk of end-organ damage. Patients with hypertensive emergency require admission to an intensive care unit (ICU), intravenous (IV) antihypertensive agents, and continuous BP monitoring. Based on the Seventh Report of the Joint National Committee (JNC-7) guidelines, the generalized BP goal is to lower the mean arterial pressure (MAP) by 20–25% within the first hour while avoiding excessive decreases in BP. When the patient is stable, the SBP can be lowered to 160 mm Hg, and DBP can be lowered to 100–110 mm Hg within the next 2–6 h. If this level of BP control is tolerated and the patient is stable, a gradual reduction to the patient's baseline BP can be achieved over the next 24–48 h [48, 49, 53]. There are exceptions to the generalized BP goal for patients who have hypertensive emergencies. This includes patients with certain complications such as acute aortic dissection, acute intracerebral hemorrhage, and acute ischemic stroke, with or without reperfusion therapy. The specific blood pressure goals are listed in Table 48.5 [48, 49, 52, 54, 55].

Table 48.4 Common antihypertensive agents used for hypertensive urgencies [32, 48, 52]

Agent	MOA	Dose	Onset	Duration	Common adverse effects[a]
Captopril	ACE inhibitor	12.5–50 mg PO every 1–2 h	15–30 min	4–6 h	Acute renal failure Angioedema Cough
Clonidine	Central α_2-agonist	0.1–0.2 mg PO every 1–2 h	30–60 min	6–8 h	Bradycardia Dry mouth Rebound hypertension after withdrawal Sedation
Furosemide	Loop diuretic	20–40 mg PO every 2–3 h	30–60 min	8–12 h	Hypokalemia Hyponatremia Volume depletion
Labetalol	A_1, β[beta]$_{1\&2}$-blocker	200–400 mg PO every 2–3 h	30–120 min	6–8 h	Bronchoconstriction Heart block Heart failure Hypotension Vomiting
Nitroglycerin 2%	Nitrate	1–2 inches topically every 6 h	20–60 min	4–8 h	Bradycardia Dizziness Headache Methemoglobinemia

ACE angiotensin-converting enzyme, *MOA* mechanism of action, *PO* per os, by mouth
[a]Hypotension can occur with all agents

Table 48.5 Agents for treating hypertensive emergencies with comorbidities and blood pressure goals [48, 49, 52, 54, 55]

Comorbidity	Preferred agent(s)[a]	Blood pressure goal
Acute aortic dissection	Esmolol[b]	SBP <120 mm Hg and heart rate <60 beats/minute within 20 min; lowest BP possible that maintains end-organ perfusion (SBP 70–90 mm Hg)
Acute heart failure (pulmonary edema)	Loop diuretics Nitroglycerin Nitroprusside	Generalized goal[c]
Acute ischemic stroke	Clevidipine Labetalol Nicardipine Nitroprusside	Ineligible for reperfusion therapy: <220/120 mm Hg, decrease no more than 15%
		Eligible for reperfusion therapy: <185/110 mm Hg
		During and post-reperfusion therapy for at least 24 h: <180/105 mm Hg
		Planned mechanical thrombectomy and have not received IV fibrinolytic therapy: <185/110
		During and post mechanical thrombectomy for 24 h: <180/105 mm Hg
Acute intracerebral hemorrhage	Clevidipine Labetalol Nicardipine Nitroprusside	SBP 150–220 mm Hg: Acute lowering of SBP to140 mm Hg is probably safe
		SBP >220 mm Hg: May be reasonable to consider aggressive reduction
Acute myocardial infarction	Clevidipine[d] Esmolol/labetalol Nicardipine[d] Nitroglycerin	Generalized goal[c]
Acute renal failure	Clevidipine Fenoldopam Nicardipine	Generalized goal[c]

BP blood pressure, *CPP* cerebral perfusion pressure, *ICP* intracranial pressure, *MAP* mean arterial pressure, *mm Hg* millimeters of mercury, *SBP* systolic blood pressure
[a]Agents are listed in alphabetical order, not in preference
[b]β[beta]-blockade must be used prior to other vasodilators
[c]Decrease MAP by 20–25% during first hour; if patient is stable, decrease SBP to 160 mm Hg and DBP to 100 mm Hg over next 2 to 6 h, then a gradual reduction to the patient's baseline BP over the next 24 to 48 h
[d]May be used in patients with heart rate <70 beats/min

Table 48.6 Common parenteral agents used for hypertensive emergencies [32, 48, 49]

Agent	MOA	Bolus dose	Continuous infusion dose	Dose titration	Onset	Duration	Adverse effects[a]
Clevidipine[b]	Calcium channel blocker	Not applicable	1–16 mg/h	1 mg/h every 2 min	2–4 min	5–15 min	Flushing Headache Heart failure Tachycardia
Esmolol	β[beta] $_1$-blocker	250–500 mcg over 1 min; may repeat after 5 min	25–300 mcg/kg/min	25 mcg/kg/min every 5 min	1–2 min	10–30 min	Bronchoconstriction Heart block Heart failure
Fenoldopam[c]	Dopamine-1 receptor agonist	Not applicable	0.1–1.6 mcg/kg/min	0.05–0.1 mcg/kg/min every 15 min	5–10 min	10–15 min	Flushing Headache Tachycardia
Labetalol	α[alpha]$_1$, β[beta]$_{1\&2}$-blocker	20–80 mg over 2 min every 10 min	2–8 mg/min; max dose for bolus and infusion is 300 mg/24 h	Titrate by 0.5 mg/min every 60 min	5–10 min	2–6 h	Bronchoconstriction Heart block Heart failure Vomiting
Nicardipine	Calcium channel blocker	Not applicable	5–15 mg/h	2.5 mg/h every 5 min	5–10 min	2–4 h	Flushing Headache Reflex tachycardia
Nitroglycerin	Converts to NO and increases cGMP	Not applicable	5–200 mcg/min	5–10 mcg/min every 5 min	1–3 min	5–15 min	Headache Methemoglobinemia Tachycardia Vomiting
Sodium nitroprusside[d]	Increase cGMP, blocks intracellular calcium	Not applicable	0.25–10 mcg/kg/min	Titrate by 0.5 mcg/kg/min every 5 min	Immediate	1–2 min	Cerebral auto regulation impairment Coronary steal Cyanate toxicity Nausea/vomiting

cGMP cyclic guanosine monophosphate, *h* hour, *kg* kilogram, *mcg* micrograms, *mg* milligrams, *min* minute, *MOA* mechanism of action, *NO* nitric oxide

[a]Hypotension may occur with all agents

[b]Caution with severe aortic stenosis and acute heart failure

[c]Caution with glaucoma and sulfite allergies

[d]Caution with high intracranial pressure, hepatic and renal failure

Treatment decisions with parental agents should focus on the end-organ system at risk and associated side effects caused by the specific agent used. See Table 48.5 [48, 49, 52, 54, 55] and Table 48.6 [32, 48, 49] for recommended intravenous agents per end-organ system.

Aortic Dissection Acute aortic dissection has a high mortality rate of 1% per hour over the first several hours [56]. Early diagnosis and treatment is crucial for survival. Intravenous, fast-acting β-blockers are the drug of choice due to their ability to lower the heart rate and reduce aortic stress [57].

Heart Failure Patients with heart failure, severe hypertension, and significant fluid overload should be treated initially with intravenous loop diuretics to reduce mortality [58]. Nitroglycerin and sodium nitroprusside are the most commonly used antihypertensive agents to help with filling pressures and left ventricular afterload [58].

Ischemic Stroke Appropriate management for ischemic stroke is very important. Studies have demonstrated a "U-shaped" relationship between BP and clinical outcome [59]. The concern with lowering the BP in patients with ischemic stroke is expansion of the central ischemic core. Cerebral autoregulation can be lost after a stroke, leaving the core, and the surrounding ischemic penumbra, prone to hypoperfusion and a potentially worse outcome [60]. There are limited studies evaluating the optimal BP goal and appropriate pharmacotherapy. Modest lowering of the BP is recommended and dependent on the patient's eligibility for reperfusion therapy [52].

Several small studies have compared labetalol to nicardipine for lowering BP. In a meta-analysis, these two agents had comparable side effects and efficacy for the treatment of hypertension in patients with several different types of strokes, including acute ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage [61]. In a more recent study, intravenous labetalol and nicardipine continuous infusions were comparable with no significant difference in time to BP goal, variability in BP, and use of rescue antihypertensive medications [62].

Hemorrhagic Stroke The most acute concern after hemorrhagic stroke is hematoma volume expansion [63]. Hematoma expansion occurs very early (first 3 h), with limited expansion beyond 24 h [59]. Two studies have confirmed the feasibility and safety of early rapid BP lowering in patients with intracerebral hemorrhage (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial [INTERACT] pilot study and the Antihypertensive Treatment in Acute Cerebral Hemorrhage [ATACH] trial) [64, 65]. Labetalol and nicardipine are used to control BP in patients with hemorrhagic stroke as mentioned in the ischemic stroke section. Clevidipine is also used to lower BP in patients with a hemorrhagic stroke. No difference in safety and efficacy was found when compared to nicardipine [66–68].

Acute Coronary Syndromes The goal for patients experiencing acute coronary syndrome is to decrease myocardial oxygen demand and improve coronary perfusion. For patients experiencing hypertensive emergencies, both nitrates and β-blockers have been used to reach the above goal [69].

Renal Failure Fenoldopam has an indication for hypertensive emergencies and improves creatinine clearance, urine flow rates, and sodium excretion in severely hypertensive patients with both normal and impaired renal function [49, 66]. Therefore, it may be useful in patients with hypertensive emergencies and renal failure. Diuretic use in patients with severe hypertension and renal failure may be either beneficial or harmful and is completely dependent on the patient's volume status.

It is absolutely crucial to recognize hypertensive emergencies as soon as possible. End-organ damage can be minimized by early diagnosis and treatment. Treatment and the BP goal are dependent on the end-organ involved.

Nausea and Vomiting

Chemotherapy-induced nausea and/or vomiting (CINV) is a debilitating side effect of chemotherapy, potentially impacting fluid and electrolyte balance, nutrition status, future treatment courses, quality of life, and overall cost of healthcare. Direct healthcare costs of treating CINV per day can range from US$1300 to US$2400, not accounting for indirect costs associated with lost workdays or productivity losses [70]. After the introduction of serotonin (5-HT_3) receptor antagonists, prophylactic antiemetic regimens were able to reduce the incidence of CINV. Despite the improvement, CINV refractory to these prophylactic regimens occurs in up to 40% of patients receiving chemotherapy [71]. CINV can be characterized as acute, delayed, breakthrough, refractory, or anticipatory. This section will focus on management strategies for breakthrough CINV only.

Pathophysiology

CINV is initiated by the peripheral stimulation of enterochromaffin cells in the GI tract and the central stimulation of the chemoreceptor trigger zone by chemotherapeutic agents. Centrally, substance P release, which is triggered by chemotherapy, binds to NK-1 receptors and stimulates the chemotherapeutic trigger zone. Peripherally, stimulation of enterochromaffin cells causes a release of serotonin (5-HT), which sends information to the central nervous system [71, 72]. These signals are received and processed by the vomiting center in the medulla oblongata, which are then converted to signals promoting emesis [73, 74]. Serotonin is the predominant peripheral neurotransmitter involved in the first 24 h of CINV, while signals from dopamine and substance P (which corresponds with the primarily centrally located neurokinin-1 receptor) predominate after 24 h [75]. Other neurotransmitters and receptors involved include acetylcholine, corticosteroid, cannabinoid, histamine, neurokinin, and opioid [76].

Clinical Features

Nausea is an unpleasant sensation in the back of the throat or epigastrium that may or may not result in emesis. Vomiting is a motor reflex, which results in a forceful expulsion of GI contents [73, 74]. CINV can be categorized into acute and delayed phases. Acute CINV occurs within the first 24 h of chemotherapy, while delayed CINV occurs after 24 h and can last up to 7 days. Breakthrough CINV is any nausea or vomiting that occurs despite optimal prophylactic antiemetic regimens [76].

Chemotherapy Agents Implicated

Chemotherapeutic agents are classified into four different categories based on their emetogenicity risk. Highly emetogenic agents have a risk of greater than 90% (meaning 90% or more of patients receiving these agents will experience emesis without prophylactic antiemetics), moderately emetogenic agents have a risk of 30–90%, agents with low emetogenicity have a risk of 10–30%, and minimally emetogenic agents have a risk of less than 10% for emesis [77]. Other risk factors for CINV include female sex, younger age, history of little to no alcohol use, history of CINV or morning sickness during pregnancy, and susceptibility to motion

sickness. A chart grouping chemotherapy agents by emetogenicity risk can be found in the National Comprehensive Cancer Network (NCCN) guidelines [76].

Treatment

Treatment of breakthrough CINV is more challenging than preventing CINV. There are currently three published guidelines from three different cancer organizations—NCCN, American Society of Clinical Oncologic (ASCO), and Multinational Association of Supportive Care in Cancer/European Society for Medical Oncologic (MASCC/ESMO) [76, 78, 79]. NCCN provides the most comprehensive recommendations for breakthrough CINV. NCCN recommends using an agent different from those in the prophylactic regimen and suggested that multiple agents with different mechanisms of action may be needed. There is also a recommendation to utilize these agents on a scheduled, around-the-clock dosing strategy versus an as-needed basis. Therapeutic options include benzodiazepines, dopamine antagonists (including phenothiazines, olanzapine, haloperidol, and metoclopramide), cannabinoids, antihistamines/anticholinergics, corticosteroids, and serotonin receptor subtype 3 (5-HT_3) antagonists. Additionally, it may be beneficial to initiate an H_2 antagonist or proton pump inhibitor to treat concurrent dyspepsia, as well as maintain optimal hydration status and electrolyte balance [76]. See Table 48.7 [72, 73, 75, 76, 80–82] for details on pharmacotherapeutic treatment options for CINV. Beyond a small, phase 2 trial [83], neurokinin 1 (NK-1) receptor antagonists such as aprepitant have been studied primarily as part of prophylactic regimens and have not been recommended by any of the three main antiemesis guidelines from ASCO, NCCN, or MASCC/ESMO for the treatment of breakthrough CINV [76, 78, 79]. Aside from guideline recommendations, considerations such as previous success with certain antiemetic classes, drug–drug interactions, and patient-specific characteristics (e.g., allergies or QTc interval) should all be taken into account when selecting an antiemetic regimen for breakthrough CINV.

There is currently a paucity of literature to guide the practitioner in selecting antiemetics for breakthrough CINV. The majority of recent data highlights the antipsychotic, olanzapine. Likely due to its effect on multiple receptor sites involved in the pathophysiology of CINV, olanzapine has shown to be beneficial in treating breakthrough CINV [76].

One retrospective study observed 33 patients who experienced refractory CINV that failed to respond to both benzodiazepines and dopamine antagonists and received at least one dose of olanzapine. Of these patients, 65–70% had success with olanzapine. The typical dose given was 5–10 mg by mouth daily for a median of 4 days [75]. Another observational study evaluated medications received for breakthrough CINV. Of 39 patients who required rescue antiemetics, 88% received prochlorperazine, while 12% received a 5-HT_3 antagonist. Both groups reported a 75% reduction of nausea after 4 h. Both groups also noted significant symptom control within 30 min [84]. In one of the only randomized controlled trials evaluating treatment for CINV, Navari et al. studied 108 patients receiving either olanzapine or metoclopramide for breakthrough CINV. Patients were included if they received highly emetogenic chemotherapy with appropriate prophylactic antiemetic regimens. Olanzapine was given as a 10 mg dose orally every 24 h for 72 h, while metoclopramide was given as a 10 mg dose orally every 8 h for 72 h. Patients receiving olanzapine had a significantly lower incidence of both nausea and vomiting, and olanzapine was well tolerated [85]. In a retrospective study by Chiu et al., olanzapine was evaluated in 193 cases of breakthrough CINV and was found to improve nausea 88.1% of the time and vomiting 21.8% of the time. Several adverse effects were reported including sedation (42% of cases) and constipation (32% of cases). Of note, the majority of patients in this trial (94%) received a lower dose of olanzapine at 2.5 mg daily [86]. Lastly, Nakagaki et al. randomized 62 stem cell transplant patients (following chemotherapy) to ondansetron 32 mg infused over 24 h, olanzapine 10 mg daily + ondansetron IV three times daily, or a single dose of palonosetron 0.25 mg IV. The primary composite outcome of no emesis, no rescue medication use, and improvement in nausea by ≥50% was significantly higher in the olanzapine + ondansetron group at 24 h (45% versus 6% in the ondansetron infusion group and 18% in the palonosetron group) and at 48 h (64% versus 6% in the ondansetron infusion group and 18% in the palonosetron group) [87]. With growing evidence supporting olanzapine use in the treatment of breakthrough CINV, NCCN recommends treatment of CINV with olanzapine as a category 1 recommendation (unless olanzapine was used as part of the prophylactic regimen) [76].

CINV continues to be a significant adverse effect of chemotherapy that can impact the treatment of cancer. Utilizing the most effective prophylactic regimens based on the emetogenicity of the chemotherapy agent(s) is most important, but patients may still develop breakthrough CINV. In these cases, it is important to quickly control symptoms with scheduled antiemetics that have mechanisms differing from initial agents used for prophylaxis.

Nephrotoxicity

Chemotherapy-induced nephrotoxicity (CIN) is a significant complication of therapy, resulting in treatment delays, dosage reductions, and therapy discontinuation. In 2015, the International Serious Adverse Event Consortium report classified drug-induced kidney disease into four main

Table 48.7 Pharmacologic treatment options for breakthrough chemotherapy-induced nausea and vomiting (CINV) [72, 73, 75, 76, 80–82]

Agent	Dose	MOA	Adverse effects	Comments
5-HT_3 Receptor Antagonists				
Ondansetron	16–24 mg PO daily or 8–16 mg IV	Antagonistic effect at the 5-HT_3 receptor located in the GI tract, CTZ and vomiting center	QTc prolongation Headache Constipation	PO and IV are equally effective All are equally effective/safe when given in biologically equal doses If palonosetron was used in the prophylactic regimen, a different mechanism should be targeted for breakthrough CINV Most benefit seen when administered around-the-clock (scheduled) PO ondansetron has less QTc prolongation risk than IV
Dolasetron	100 mg PO daily			
Granisetron	1–2 mg PO daily or 1 mg PO twice daily or 0.01 mg/kg (maximum 1 mg) IV daily or 3.1 mg/24-h TD patch every 7 days			
Dopamine antagonists				
Haloperidol	0.5–2 mg PO/IV every 4–6 h	Butyrophenone, most potent dopamine antagonist; weak anticholinergic and alpha-1 adrenergic blocking effects	Sedation QT_c prolongation Dystonic reactions Extrapyramidal symptoms	Antiemetic properties seen at doses lower than antipsychotic doses
Metoclopramide	10–20 mg PO/IV every 4–6 h	Benzamide analog, peripheral dopamine antagonist; stimulates prokinesis via serotonin (5-HT_4) receptors	Dystonic reactions Tardive dyskinesia Akathisia Diarrhea Mild sedation Orthostatic hypotension	Increased efficacy at higher doses due to additional serotonin blockade Tardive dyskinesia risk is cumulative dose-dependent and more likely to occur with chronic use
Prochlorperazine	10 mg PO/IV every 6 h (max 40 mg/day) or 25 mg PR twice daily	Phenothiazine; dopamine antagonist; some anticholinergic and alpha-adrenergic blocking effects; prochlorperazine with more predominant dopamine antagonism; promethazine with more antihistamine properties	Sedation Dystonic reactions Extrapyramidal symptoms	Due to increased histamine receptor antagonism, promethazine causes more sedation than prochlorperazine
Promethazine	12.5–25 mg PO/IV every 4–6 h or 25 mg PR every 6 h			
Olanzapine	5–10 mg PO daily	Effects on multiple receptors (serotonin, dopamine, acetylcholine, muscarinic, histamine, alpha-1 adrenergic)	Sedation Orthostatic hypotension Increased appetite Dystonic reactions	Administer at bedtime to avoid daytime sedation Consider dose reduction (to 5 or 2.5 mg if higher dose causes excessive sedation) Sedation improves after day 2
Cannabinoids				
Dronabinol	5–10 mg capsule PO every 6–8 h	Effects on the cannabinoid receptors in the CNS and peripheral receptors	Sedation Dizziness Dysphoria Postural hypotension Hallucinations Appetite stimulation	Use is limited by side effects Titrate dose upward to minimize side effects Dronabinol oral solution has greater bioavailability than the capsule (2.1 mg oral solution = 2.5 mg capsule)
Nabilone	1–2 mg PO twice daily			
Benzodiazepines				
Lorazepam	0.5–2 mg PO/IV every 6 h	Binds to benzodiazepine receptors in the postsynaptic GABA receptors	Sedation Respiratory depression Hypnosis/amnesia	Added benefit of reducing anxiety Not recommended as monotherapy Caution when used with opioids

(continued)

Table 48.7 (continued)

Agent	Dose	MOA	Adverse effects	Comments
Corticosteroids				
Dexamethasone	12 mg PO/IV daily	Not fully understood	Insomnia Increased appetite Hyperglycemia GI distress	Is more commonly used in prophylactic regimens for CINV Administer in the morning to alleviate insomnia side effect
Other Agents				
Scopolamine patch	1.5 mg TD every 72 h	Antimuscarinic, anticholinergic	Sedation Fatigue Paradoxical CNS excitation Hallucinations Xerostomia	May benefit if CINV caused by excessive secretions or includes component of motion sickness

CNS central nervous system, *CTZ* chemotherapy trigger zone, *GABA* gamma-aminobutyric acid, *GI* gastrointestinal, *IV* intravenous, *kg* kilogram, *mg* milligrams, *MOA* mechanism of action, *PO* by mouth, *PR* per rectum or rectally, *TD* transdermal

types: acute kidney injury (AKI), glomerular disorder, tubular disorder, or nephrolithiasis/crystalluria. AKI is further broken down to acute tubular necrosis (ATN), acute interstitial nephritis (AIN), and osmotic nephrosis [88]. Chemotherapy can affect any area of the kidney including the glomerulus, tubules, interstitium, or microvasculature. Adverse effects may range from a simple rise in serum creatinine without other sequelae to acute kidney failure requiring dialysis [89].

Risk Factors

Several factors increase the risk of CIN including intravascular volume depletion due to fluid losses such as vomiting or diarrhea or fluid shifts as in ascites; urinary tract obstruction due to tumor involvement; and/or intrinsic renal disease related to diabetes, hypertension, or chronic heart failure [89]. Exposure to concomitant nephrotoxic agents (e.g., acyclovir, allopurinol, aminoglycosides, amphotericin B, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, contrast agents, diuretics, foscarnet, ganciclovir, lithium, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, sulfonamides, tacrolimus, and vancomycin) also increases the risk of acute kidney injury [88]. The following section discusses chemotherapy agents most commonly associated with kidney injury.

Chemotherapy Agents Implicated

Platinum-Based Compounds

Nephrotoxicity is a major dose-limiting side effect of cisplatin occurring in about 30% of patients. Nephrotoxicity results from tubular epithelial cell toxicity, vasoconstriction, and proinflammatory effects. These effects are due to a chloride ion in the cis position. Carboplatin and oxaliplatin do not contain this chloride and consequently are less nephrotoxic. The renal dysfunction manifests as hypomagnesemia, salt wasting, a Fanconi-like syndrome, and anemia which can progress and potentially be irreversible [89]. To minimize CIN, intravenous hydration, mannitol, and amifostine can be used [90, 91].

Alkylating Agents

Hemorrhagic cystitis (HC) can result from administration of cyclophosphamide or ifosfamide. The toxic metabolite, acrolein, is filtered by the kidneys and then concentrates in the bladder, inducing an inflammatory response. In addition, chloroacetaldehyde, a major metabolite of ifosfamide, is toxic to tubular cells [89]. Forced saline diuresis and mesna can be used to prevent HC in patients receiving high-dose cyclophosphamide or ifosfamide. Patients should be instructed to drink fluids and void at first sensation as well as void at least once during the night [91]. Both agents can also cause syndrome of inappropriate antidiuretic hormone (SIADH) which results in hyponatremia. In addition, ifosfamide can cause Fanconi syndrome, characterized by a global transport defect in the proximal tubule of the kidney, and cause hypophosphatemia, polyuria, acidosis, hypokalemia, glycosuria, and proteinuria [90].

Antitumor Antibiotic

Renal toxicity with mitomycin can occur in up to 10% of patients and manifests as hemolytic uremic syndrome (HUS), resulting in thrombotic microangiopathy (TMA) from direct endothelial injury. The renal failure develops slowly and is usually associated with hypertension [89, 92].

Antimetabolites

High-dose methotrexate causes AKI in about 2% of patients secondary to ATN resulting from crystallization of the par-

ent drug and metabolites within the kidney. The AKI is usually reversible and can be minimized by ensuring appropriate hydration and high urine flow with urinary alkalinization (pH >7.0) [89]. Leucovorin is often given with high-dose methotrexate to reduce toxicities [90]. Pemetrexed has been associated with AKI, ATN, renal tubular acidosis, and diabetes insipidus. AKI is usually reversible upon drug discontinuation, but irreversible AKI and interstitial fibrosis have been reported [89, 93]. Gemcitabine may induce TMA through direct endothelial injury. It can also be caused by an immune-mediated mechanism, and if this is the case, the drug must be avoided for life [89, 93].

Targeted Therapy

Magnesium wasting is a major adverse effect of cetuximab therapy. Cetuximab is an antagonist of the epidermal growth factor receptor (EGFR). EGFR causes downregulation of the transient receptor potential cation channel, subfamily, member 6 (TRPM6), which results in magnesium wasting [94]. The hypomagnesemia usually resolves after drug discontinuation. To prevent adverse effects of hypomagnesemia, oral and/or intravenous replacement is necessary [89, 95].

Electrolyte Disorders

Electrolyte derangements are prevalent in cancer patients and can occur for a multitude of reasons. A common cause of fluid and electrolyte abnormalities in cancer patients is dehydration due to nausea, vomiting, diarrhea, or decreased appetite. Other reasons include tumor lysis syndrome, medication adverse effects, acute kidney injury, or complications of the cancer itself. Common electrolyte abnormalities in cancer patients are hyponatremia, hypomagnesemia, and hypo- or hyperkalemia [96]. Though many electrolyte abnormalities may not result from chemotherapeutic agents, many agents are well known to cause significant electrolyte disturbances, which will be the focus of this section. A detailed description of electrolyte disorders and chemotherapy agents implicated can be seen in Table 48.8 [97–100].

Pathophysiology

The mechanism by which chemotherapeutic agents cause electrolyte abnormality differs with each agent, ranging from renal wasting to direct tubular damage. Pathophysiologic details pertaining to each agent will be discussed within the sections below.

Chemotherapy Agents Implicated

Platinum-Based Chemotherapy

Platinum-based chemotherapeutic agents cause a wide variety of electrolyte abnormalities including hypomagnesemia, hypocalcemia, hypokalemia, and hyponatremia. Of all the platinum-based agents, cisplatin causes the most profound electrolyte disturbances, of which hypomagnesemia is most prevalent, occurring in up to 90% of patients [98]. The incidence appears to be dose-related and was found to reach 100% after the sixth cycle of chemotherapy in one study [101]. Hypomagnesemia occurs due to proximal tubular necrosis caused by cisplatin at the site of magnesium reabsorption, resulting in renal magnesium wasting [102]. Hypokalemia can also occur in the same manner [98].

Cisplatin-induced hypomagnesemia persists in many patients, up to years after cisplatin discontinuation [103]. Due to its high incidence of nephrotoxicity, cisplatin administration is usually preceded by judicious hydration with intravenous fluids. This induces an osmotic diuresis, which increases urinary magnesium excretion and can worsen hypomagnesemia [104]. Most patients are asymptomatic; however, muscle weakness and cramping, tetany, fatigue, seizures, arrhythmias, paralysis, and neurotoxicity can occur [98, 105]. Even if asymptomatic, it is important to correct because low serum magnesium can lead to refractory hypokalemia and hypocalcemia [98, 104, 106]. The persistence of hypomagnesemia has even been associated with decreased survival in ovarian cancer patients [95].

In addition to hypomagnesemia, hypokalemia, and hypocalcemia, platinum agents can also cause hyponatremia (in up to 43% treated with cisplatin) [98]. In a pharmacovigilance study where 19,901 adverse event reports were evaluated in non-small cell lung cancer patients, hyponatremia and hypokalemia were significantly associated with carboplatin exposure [107]. SIADH and renal salt wasting are likely the mechanisms by which platinum-based agents cause hyponatremia [98, 108]. Salt wasting can occur because of direct tubular damage from cisplatin, leading to a disruption in sodium and water reabsorption. This syndrome has been reported to occur in up to 10% of patients. One important consideration is to ensure an accurate diagnosis of hyponatremia, as treatment for SIADH and salt wasting syndrome differs significantly (free water restriction for the former and volume repletion for the latter) [108].

Cyclophosphamide

Hyponatremia resembling SIADH induced by cyclophosphamide was initially and is more commonly reported with high doses (30–50 mg/kg) [98]. However, this adverse effect has been reported with moderate doses and doses as low as 500 mg/m^2 and 10 mg/kg and even after a single dose of

Table 48.8 Electrolyte disorders and chemotherapy agents implicated [97–100]

Electrolyte disorder	Agents	Mechanism	Clinical presentation	Treatment[a]
Hyponatremia (serum sodium <135 mEq/L)	Carboplatin Cisplatin Ifosfamide	Renal salt wasting or SIADH	Headache Nausea/vomiting Confusion Seizures Hypovolemic if renal salt wasting Euvolemic if SIADH	Renal salt wasting: Volume repletion with PO/IV sodium chloride supplementation SIADH: Fluid restriction Can consider low-dose diuretics Can consider oral sodium chloride If severe or acute symptoms, consider initial management with hypertonic, 3% sodium chloride infusion at a rate of 15–80 mL/h, or up to 1–2 mL/kg/hour with frequent sodium monitoring
	Interferon Levamisole Melphalan Vinblastine Vincristine Vinorelbine	SIADH		
	Cyclophosphamide	SIADH or water intoxication		
	Methotrexate	Alteration in body fluid volumes		
Hypomagnesemia (serum magnesium <1.5 mg/dL)	Cetuximab Cisplatin Carboplatin Oxaliplatin Ifosfamide	Magnesium wasting (impaired reabsorption of magnesium in the kidneys)	Muscle cramps and weakness Paresthesias Tetany Tremulousness Arrhythmias Seizures	PO[b]/IV magnesium supplementation (e.g., magnesium oxide for PO, magnesium sulfate for IV) Mild to moderate hypomagnesium (1.0–1.5 mg/dL): 8–32 mEq Severe hypomagnesemia (<1.0 mg/dL): 32–64 mEq
Hypokalemia	Azacitidine Cisplatin Ifosfamide Streptozocin	Renal losses via renal tubular acidosis, Fanconi syndrome, or secondary to hypomagnesemia	Weakness Constipation EKG changes Arrhythmias	PO/IV potassium supplementation (e.g., potassium chloride) Mild to moderate hypokalemia (2.5–3.4 mEq/L): 20–40 mEq Severe hypokalemia (<2.5 mEq/L): 40–80 mEq Ensure adequate repletion of magnesium
	Abiraterone	Excessive mineralocorticoid activity		
Hypophosphatemia (serum phosphorus <2.7 mg/dL)	Azacitidine Ifosfamide Streptozocin	Proximal tubular damage impairing reabsorption of phosphorus, Fanconi syndrome	Respiratory distress Weakness Paresthesias Neurologic dysfunction Seizures	PO/IV phosphorus supplementation (i.e., sodium phosphate or potassium phosphate) Mild hypophosphatemia (2.3–2.7 mg/dL): 0.08–0.16 mmol/kg Moderate hypophosphatemia (1.5–2.2 mg/dL): 0.16–0.32 mmol/kg Severe hypophosphatemia (<1.5 mg/dL): 0.32–0.64 mmol/kg
Hypocalcemia (corrected serum calcium[c] <8.6 mg/dL)	Cetuximab Cisplatin	Potentially secondary to hypomagnesemia (causing impaired parathyroid function) or via renal losses	Tetany Seizures	PO/IV calcium supplementation (e.g., calcium carbonate for PO, calcium gluconate for IV) Mild to moderate/asymptomatic: Calcium gluconate 1–2 g IV or PO supplementation Severe/symptomatic: Calcium chloride[d] 1 g IV or calcium gluconate 3 g IV Ensure adequate repletion of magnesium

CrCl creatinine clearance, *DMSO* dimethyl sulfoxide, *IV* intravenous, *mg* milligrams, *SC* subcutaneous

[a]Treatment recommendations are for patients with normal renal function; for patients with impaired renal function, administer 50% or less of the recommended dose

[b]PO magnesium may cause diarrhea, especially in larger doses

[c]Corrected serum calcium = serum calcium + (0.8 × [4 − serum albumin])

[d]Requires administration via central IV access because extravasation may cause tissue necrosis

[a]Some literature suggests using cold compresses with taxanes

500 mg [83, 109]. Cyclophosphamide-associated SIADH is postulated to be caused by either an antidiuretic hormone (ADH)-like metabolite or a direct toxic effect on the renal distal tubule by cyclophosphamide or one of its metabolites [97, 110]. Hyponatremia presents variably depending on the acuity and severity, causing symptoms ranging from headache, nausea, and vomiting to altered mental status, seizures, and coma [99]. SIADH in this setting generally occurs 4–12 h after drug administration and usually resolves within 24 h of drug discontinuation [97]. Treatment for SIADH

centers on fluid restriction, but this may be challenging due to the recommendation for generous hydration to prevent cyclophosphamide-induced hemorrhagic cystitis [105].

Vinca Alkaloids

Of the vinca alkaloids, vincristine poses the highest risk of hyponatremia. This hyponatremia is thought to resemble SIADH and involves an inappropriate release of antidiuretic hormone in the setting of hypotonic hyponatremia [105]. The incidence is 1.3 in 100,000 treated patients and can be up to 44% of treated patients when given with azole antifungals due to a drug–drug interaction [98, 111]. The onset of hyponatremia occurs 1–2 weeks after administration and usually lasts for 2 weeks but can last up to 30 days. Hyponatremia induced by vinca alkaloids is usually reversible with proper treatment, but fatalities have been reported [97].

Ifosfamide

Fanconi syndrome is a well-known adverse effect of ifosfamide therapy as previously discussed [98, 112]. Fanconi syndrome involves damage to the proximal tubules resulting in impairment of electrolyte reabsorption, including phosphorus, bicarbonate, and glucose. The predominant concern is hypophosphatemia, which can be severe enough to cause rickets in the pediatric population [112]. Other signs and symptoms of hypophosphatemia include respiratory distress, neurologic dysfunction, and seizures [99]. Several risk factors for ifosfamide nephrotoxicity have been identified, including high cumulative doses of ifosfamide, concomitant cisplatin use, and nephrectomy [112]. Lastly, ifosfamide may also cause hypokalemia through renal wasting [98]. It is also important to note that manifestations of ifosfamide toxicities may not appear until years following therapy.

Cetuximab

Cetuximab was shown to cause hypomagnesemia in over 11% of patients in one retrospective study. Patients receiving a concomitant platinum-based agent had a more rapid and more significant decrease in magnesium levels at the end of 12 weeks [113]. The mechanism underlying cetuximab-induced hypomagnesemia appears to be impaired reabsorption of magnesium due to cetuximab's inhibition of epidermal growth factor receptor (EGFR), which aids in magnesium transport, thus resulting in magnesium wasting [114]. Although severe hypomagnesemia occurs in only 11% of patients, it has been shown that nearly half of patients who receive cetuximab develop some degree of hypomagnesemia [113]. Oftentimes, hypomagnesemia due to cetuximab use is refractory to oral magnesium replacement and requires intravenous replacement. Another study showed variable rates of hypomagnesemia based on cancer-type with non-small cell lung cancer at the highest risk and colorectal cancer at the lowest risk [115]. Interestingly, hypomagnesemia was shown to be predictive for delayed disease progression and improved survival in colorectal cancer patients [114].

Treatment

It is important to be cognizant of the common electrolyte disorders that can occur with chemotherapy in order to monitor serum electrolytes accordingly. Treatment of chemotherapy-induced electrolyte disorders requires vigilant monitoring and judicious replacement or correction when warranted. Oftentimes, the culprit for the electrolyte disorder is difficult to pinpoint due to confounders such as concomitant medications and disease processes, GI losses from vomiting or diarrhea, dehydration, and poor nutrition status. When identified, treatment of these electrolyte disorders usually requires only replacement or correction of balance of water and electrolytes (e.g., fluid restriction for SIADH hyponatremia) but may require alterations in therapy such as chemotherapy dose reductions, transitioning to alternative agents within the same class, changing the administration schedule, or even discontinuing the agent. When replacing electrolytes such as magnesium, potassium, phosphorus, and calcium, the clinician should be mindful of the patient's renal function and adjust replacement accordingly for impaired function. Electrolytes should be replaced orally if the patient is able to tolerate oral intake and if the patient is asymptomatic or mildly symptomatic. For acute, severe, or symptomatic electrolyte disturbances, electrolyte replacement should be given intravenously. The reader is advised to refer to other references for a more detailed discussion of the treatment of electrolyte disorders [99, 116, 117].

Anaphylaxis

Patients with cancer are increasingly exposed to a wider range of chemotherapy and targeted agents. Increased exposure leads to a higher opportunity to develop severe hypersensitivity reactions such as anaphylaxis.

Pathophysiology

The exact mechanism by which hypersensitivity reactions occur is often unclear and may vary among agent [118]. Most reactions to chemotherapy and targeted agents are consistent with type I hypersensitivity based on the Gell and Coombs immunopathologic mechanism [118, 119] (see Table 48.9 [119, 120]).

Table 48.9 Types of hypersensitivity reactions [119, 120]

	Type I	Type II	Type III	Type IV
Mediated	IgE	IgG or IgM Destruction of cells	Antigen–antibody complexes	T-cell ($CD4^+$ or $CD8^+$)
Timing	Seconds to minutes Can be delayed (1–72 h)	Days	Hours to days	Delayed (2–3 days)
Reactions	Anaphylaxis Laryngeal edema Bronchospasms Cutaneous reactions Nausea Vomiting	Hemolytic anemia Thrombocytopenia	Inflammation Serum sickness Vasculitis	Dermatologic
Causes	Hay fever Food IV contrast dye Latex Vaccines Insect bites/stings Medications such as chemotherapy and targeted agents	Transfusion reactions Methylene blue Heparin	Beta-lactams Quinidine Minocycline	Organ transplant rejection Poison ivy

Clinical Features

Anaphylaxis is an allergic reaction characterized by multisystem involvement and is considered a type I mediated reaction that is seen with certain chemotherapy and targeted agents listed below. The initial symptoms of anaphylaxis are often nonspecific and include tachycardia, faintness, cutaneous flushing, urticaria, diffuse or localized pruritus, and a sensation of impending doom. These symptoms usually occur within minutes of administering the offending agent, but reactions may develop later. Biphasic or late-phase reactions that occur 1–72 h after the initial attack have been reported [121, 122].

Chemotherapy and Targeted Agents Implicated

Hypersensitivity reactions are more commonly associated with certain chemotherapeutic and targeted agents such as taxanes, platinum-containing compounds, epipodophyllotoxins, asparaginase, procarbazine, monoclonal antibodies, and, occasionally, doxorubicin and 6-mercaptopurine [120, 123]. Immediate, acute reactions from monoclonal antibodies have been reported in 5–10% of patients for rituximab, 2–3% for infliximab, and 0.6–5% for trastuzumab and have also been reported with omalizumab, natalizumab, basiliximab, abciximab, and cetuximab [123]. Hypersensitivity symptoms to taxanes usually develop in the first few minutes of the infusion and mostly occur on the first or second exposure. Platinum-containing compound reactions usually occur at the time of cancer reoccurrence or after the patient has been exposed for at least six cycles [123].

Treatment

Early and rapid assessment is crucial and every minute counts. If a patient is unresponsive and pulseless, cardiopulmonary resuscitation should begin, and the appropriate advanced cardiovascular life support (ACLS) algorithm should be used. Advanced airway management with oxygen should be established and maintained without any delay. Circulation should be supported initially with a rapid fluid challenge of 500–2000 mL of 0.9% sodium chloride [122, 124].

Epinephrine treatment is also used to help maintain circulation in patients experiencing anaphylaxis. In a Cochrane systematic review, no randomized controlled trials using epinephrine were identified. The widespread use of epinephrine in anaphylaxis is based on non-randomized studies and expert opinion and is recommended in all anaphylaxis guidelines published to date [122]. Other types of studies include fatality studies; most people who died from anaphylaxis did not receive an epinephrine injection before cardiac arrest [125].

The adult dose of epinephrine for weight-based dosing is 0.01 mg/kg, to a maximum dose of 0.5 mg intramuscularly (IM) repeated every 5–15 min, as needed for unresolved anaphylaxis symptoms [122]. Epinephrine IM injections into the lateral aspect of the thigh have been reported to provide more rapid absorption and higher plasma epinephrine levels than IM or SC administration in the arm [126]. When anaphylaxis is not responding to repeated epinephrine IM or SC doses, intravenous (IV) epinephrine should be considered [122, 127]. However, caution should be taken when using this route. In an observational study by Campbell and colleagues, they noted that all epinephrine overdoses occurred in patients receiving IV bolus, with more arrhythmia and ischemic events than with IM and SC injections [128].

Adjunctive therapy includes H_1-antihistamines, H_2-antihistamines, and glucocorticoids. None of these therapeutic modalities have rigorous evidence to support their use, and they are second-line or adjuvant therapies in most guidelines. The first-generation, H_1-antihistamine, diphenhydramine, has been used because of its availability in IV formulation and its efficacy in relieving urticaria and itching within minutes after oral or IV administration. Due to its ability to cross the blood–brain barrier readily, diphenhydramine causes drowsiness and impaired cognitive function. Diphenhydramine given orally, IM, or slow IV in a dose of 25–50 mg has been suggested [129]. There are no studies supporting administration of H_2-antihistamines or recommending one over another; however, this class of drugs has a low potential to harm and may be helpful in the management of anaphylaxis. Giving an H_2- with a H_1-antihistamine may decrease urticaria, flushing, headache, hypotension, and rhinorrhea [125].

Glucocorticoids are traditionally administered to help reduce symptoms and to prevent biphasic anaphylactic reactions that may occur. The onset of the glucocorticoid action can be anywhere from 4 to 6 h. They are not the drug of choice for the initial phase of anaphylaxis and due to low evidence are not recommended for use in the 2020 anaphylaxis practice parameter publication [122]. Figure 48.1 is an algorithm detailing steps for treating patients with signs and symptoms of anaphylaxis.

Early recognition and treatment of anaphylaxis saves lives. There is little to no supporting evidence for the treatment of anaphylaxis, but epinephrine has shown to be beneficial, and death has been associated with failure to use epinephrine before cardiac arrest.

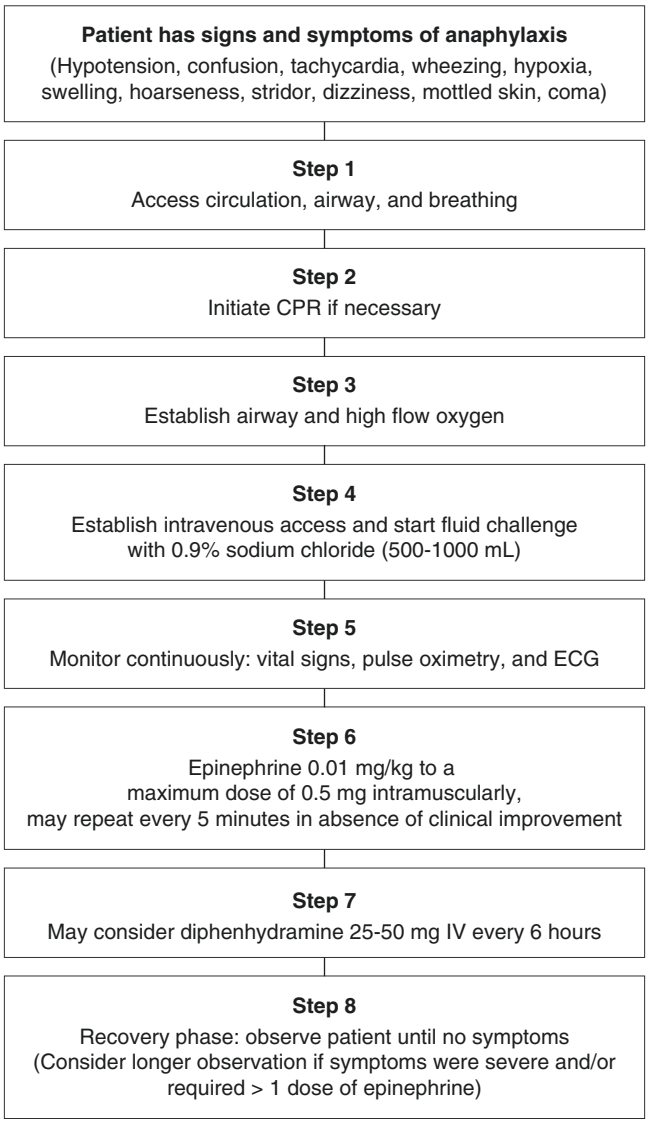

Fig. 48.1 Algorithm detailing steps for treating patients with signs and symptoms of anaphylaxis

Extravasation

Extravasation is a well-recognized complication of intravenous chemotherapy [130]. The incidence of accidental extravasation of intravenous drugs into the tissue can be anywhere from 0.1% to 6.5% [130, 131].

Clinical Features

Extravasation is the unintentional instillation, leakage, passage, or escape of fluid or drug from a blood vessel into surrounding tissue. This may result in varying degrees pain, necrosis, and tissue sloughing. The degree of tissue damage is related to the properties of the drug extravasated, the duration of tissue exposure, and the amount of drug that infiltrated [132]. Chemotherapy drugs are classified into three categories according to their potential cause of tissue damage: vesicant, irritant, and non-vesicant. A vesicant is any agent with potential to cause tissue destruction, blistering, severe injury, or tissue necrosis, when extravasated [132, 133]. An irritant is any agent that can cause inflammation or irritation characterized by aching, tightness, and phlebitis but without necrosis. Non-vesicants are drugs that rarely produce acute reactions or destroy tissue when they infiltrate.

Chemotherapy Agents Implicated

Chemotherapy agents are often classified into the above three categories (Table 48.10 [130, 131, 133–135]). Every attempt

Table 48.10 Classification of chemotherapy agents according to their vascular damage potential [130, 131, 133–135]

Vesicants	Irritants	Non-vesicants
Cisplatin[a] (if >20 mL of 0.5 mg/mL)	Arsenic trioxide[b]	Arsenic trioxide[b]
Docetaxel[a]	Bleomycin[b]	Asparaginase
Dactinomycin	Bortezomib[b]	Bleomycin[b]
Daunorubicin	Busulfan	Bortezomib[b]
Doxorubicin	Carmustine	Cladribine[b]
Epirubicin	Carboplatin	Cyclophosphamide
Idarubicin	Cladribine[b]	Cytarabine
Mechlorethamine	Cisplatin[a] (if concentration less than 0.5 mg/mL)	Fludarabine
Mitomycin C		Gemcitabine[b]
Mitoxantrone	Dacarbazine	Ifosfamide[b]
Oxaliplatin[a]	Docetaxel[a]	Interferons
Paclitaxel[a]	Etoposide	Interleukin-2
Vinblastine	Fluorouracil	Melphalan[b]
Vincristine	Gemcitabine[b]	Methotrexate
Vindesine	Ifosfamide[b]	Monoclonal antibodies
Vinorelbine	Irinotecan	Pemetrexed
	Ixabepilone	Pentostatin
	Liposomal cytarabine	Raltitrexed
	Liposomal daunorubicin	Temsirolimus
	Liposomal doxorubicin	Thiotepa[b]
	Liposomal vincristine	
	Melphalan[b]	
	Mitoxantrone[a]	
	Oxaliplatin[a]	
	Paclitaxel[a]	
	Paclitaxel, nanoparticle albumin bound	
	Plicamycin	
	Streptozocin[a]	
	Teniposide	
	Thiotepa[b]	
	Topotecan	

[a]Has been described as both an irritant and vesicant in the literature
[b]Has been described as both irritant and non-vesicant in the literature

should be made to minimize the risk of extravasation. This is a collaborative practice involving physicians, nurses, pharmacists, patients, and patients' caregivers. All healthcare professionals should adhere to institutional policies and procedures to prevent extravasation. Unfortunately, not all extravasations are preventable; however, individualized risk factors for extravasation are recognized (Table 48.11 [134, 136, 137]). All parties involved should be cognizant of the signs and symptoms of chemotherapy extravasation. These may include stinging or burning pain, as well as erythema, induration, blister, or vesicle formation. Around the injection site, there may be venous discoloration, swelling, or leakage of fluid. The flow rate of the infusion may change with increased resistance that cannot be explained. Blood return from the infusion line may be impaired or impossible [132, 134]. Chemotherapy extravasation reactions may not manifest until hours, days, or even months after the infusion has been stopped or completed [138].

Table 48.11 Patient risk factors for extravasation [134, 136, 137]

Patient associated	Others
Small and fragile veins	Insufficient training of staff, poor technique
Vascular disease, Raynaud's disease; peripheral neuropathies; peripheral vascular disease such as diabetes	Butterfly, metal, or large-gauged needles
Impaired lymph flow and venous circulation	Inadequate secured needle
Superior vena cava syndrome	Veins used adjacent to tendons, nerves, or arteries
Locally infiltrating tumors	Needle location (e.g., antecubital fossa, wrist or dorsum of hand)
Age—elderly and young at the highest risk	Inappropriate needle length
Restlessness, agitation, altered mental status, or confusion	Catheter failure
Cerebral vascular accident	Multiple attempts at cannulation
Coagulation abnormalities	Irritant and vesicant drugs
Obesity	Prolonged infusions
Prior extravasation injury	Infiltration volume
	Multiple treatments of chemotherapy agents
	Previous vinca alkaloids administration
	Radiation therapy—current or past

Treatment: Pharmacologic and Non-pharmacologic

Extravasation of chemotherapy requires prompt management. Delays in vesicant extravasation treatment can cause further tissue damage, necrosis, and pain that require surgical intervention. The type of chemotherapy, drug concentration, amount of drug extravasated, pH, and osmolarity play a role in severity of tissue injury [132]. The general approach to extravasation management is early recognition and treatment to minimize the extent of extravasation and prevent further tissue damage. For patients reporting burning, pain, or any other infusion-related issue, such as swelling, increased resistance, or leakage of fluid around the site, the chemotherapy infusion stopped immediately. The infusion site should be inspected for extravasation. Patients with extravasation due to a vesicant and any large-volume extravasation or those having worsening pain at extravasation site or evidence of ulceration or tissue necrosis should present to the ED for evaluation and consideration of plastic surgery consultation.

Institutions administering chemotherapy infusions should have policies and procedures in place to ensure early intervention for extravasations. An extravasation kit should be available in the chemotherapy infusion areas. These contain both non-pharmacologic and pharmacologic treatment supplies, including disposable syringes, small-gauged needles, cold–hot packs, gauze pads, adhesive plaster, sterile and protective gloves, and medications (e.g., dexrazoxane, dimethyl sulfoxide [DMSO] 50–99%, and hyaluronidase). Pre-prepared kits allow providers to initiate treatment in the infusion areas and minimize any delay in care.

Step 1	Stop chemotherapy infusion immediately. Leave needle in place. Identify chemotherapy agent.
Step 2	Aspirate any additional drug out of catheter with syringe. Record volume aspirated.
Step 3	Remove needle.
Step 4	Mark the area and take photo of extravasation; notify physician.
Step 5	Administer non-pharmacologic and pharmacologic treatment based on chemotherapy (see **Table 48.13**).
Step 6	Elevate limb; administer additional medications as needed for pain. Assess area for necrotic tissue; consider surgical management.

Fig. 48.2 Treatment steps that should be completed when patients present with signs and symptoms of chemotherapy extravasation [130, 134]

Figure 48.2 [130, 134] denotes all treatment steps that should be completed when patients present with signs and symptoms of chemotherapy extravasation. The infusion should be discontinued as soon as extravasation is suspected. The infusion line should be disconnected, and the needle should be left in place to allow for aspiration of residual chemotherapy. Extensive or large-volume extravasation of irritants and non-vesicants should be evaluated by a plastic surgeon for further intervention and management. Small extravasation of irritants and non-vesicants should be monitored over several days to ensure that the skin is viable and pain resolves. A plastic surgery consult is recommended if the extravasation site develops full-thickness necrosis and chronic nonhealing ulceration or if the patient experiences persistent or worsening pain [139]. Vesicants should be treated with both non-pharmacologic and pharmacologic approaches. Physicians should be notified immediately with information regarding the chemotherapy agent to ensure appropriate and prompt treatment initiation. The extravasation area should be marked with a pen to monitor for extravasation spread. If the first four steps have not been completed prior to ED presentation, it is crucial that they be completed as soon as possible.

Various non-pharmacologic and pharmacologic treatments have been utilized in the past to help minimize the damage of chemotherapy agent extravasations. Available studies report varying degrees of success in managing extravasations. It should be noted that only a handful of treatment options or "antidotes" exist that can be injected or topically applied to the affected area. Vesicant chemotherapy agents can be divided into two categories: DNA binding versus non-DNA binding (Table 48.12), and treatment options for these categories differ [130].

DNA binding vesicants, such as anthracyclines, bind to the DNA in the cells of healthy tissue and promote cell death. DNA-chemotherapy complexes are released from the dead cells in the tissue and are taken up by adjacent healthy cells via endocytosis. This process is cyclic and can continue for

Table 48.12 Classification of vesicant chemotherapy agents [130]

Classification	Examples	Pharmacologic treatment
DNA binding		
Alkylating agents	Mechlorethamine	Sodium thiosulfate
Anthracyclines	Daunorubicin, doxorubicin, epirubicin, idarubicin	DMSO or dexrazoxane
Others	Mitoxantrone, mitomycin dactinomycin	DMSO
Non-DNA binding		
Vinca alkaloids	Vinblastine, vincristine, vindesine, vinorelbine	Hyaluronidase
Taxanes	Docetaxel, paclitaxel	Hyaluronidase

weeks to months after the incident [130]. If left untreated, the cell damage spreads larger and deeper, becoming more painful with time. Debridement may be required if severe injury results in tissue necrosis. Localizing the offending agent can be achieved by cooling the area with a dry cool compress or cold gel pack. This procedure may lessen the pain by constricting vessels and preventing the offending agent from spreading to surrounding healthy tissue. There is insufficient published evidence to support the efficacy of this treatment, but it may be beneficial in reducing discomfort, burning sensation, and tenderness [136]. The next step is to neutralize the offending agent, and this will depend on the extravasated chemotherapy agent (Table 48.13 for dosing) [130, 140–144].

Non-binding DNA vesicants, such as vinca alkaloids, have an indirect effect on healthy tissue. Non-DNA-binding chemotherapy agents are metabolized in the tissue and are more easily neutralized [130]. The injury caused by these agents is localized, is mildly to moderately painful, and improves over time [145]. Local warming is preferred with this group of agents to increase blood flow to the area. Warm compresses distribute the chemotherapy agent and promotes its absorption [131]. However, some controversies have arisen regarding this technique. Some literature reports wors-

Table 48.13 Treatment after extravasation [130, 140–144]

Drug	Non-pharmacologic treatment	Pharmacologic treatment dosing
Anthracyclines	Dry cold compress (3-day course)	*Dexrazoxane* (3-day course)
Daunorubicin Doxorubicin Epirubicin Idarubicin	Immediately for 20 min and four times daily—do not apply 15 min prior to or during dexrazoxane infusion	Within 6 h: 1000 mg/m^2 (max 2000 mg) IV Day 2: 1000 mg/m^2 (max 2000 mg) IV Day 3: 500 mg/m^2 (max 1000 mg) IV Maximum dose of 2000 mg per day. Doses are 24 h apart and infused over 1–2 h in opposite arm If CrCl is less than 40 mL/min—decrease dose by 50% or *DMSO 50–99%*
		Immediately apply topically 1–2 mL with cotton swab over area twice the size of that affected and allow to air dry every 6–8 h for 7–14 days; do not apply if using dexrazoxane
Cisplatin	Dry cold compress	*Sodium thiosulfate* 1/6 M
		1/6 M = 4 mL 10% sodium thiosulfate + 6 mL water
		Inject 2 mL for each 100 mg of extravasated cisplatin through existing needle; if needle has been removed, inject 1 mL SC (0.1 mL doses clockwise around extravasation using small-gauged [25 or less] needle); may repeat SC dose several times over the next 3–4 h
Mechlorethamine	Dry cold compress	*Sodium thiosulfate* 1/6 M
		1/6 M = 4 mL 10% sodium thiosulfate + 6 mL water
		Inject 2 mL for each 1 mL of extravasated mechlorethamine into existing needle; if needle has been removed, inject 1 mL SC (0.1 mL doses clockwise around extravasation using small-gauged [25 or less] needle); may repeat SC dose several times over the next 3–4 h
Mitomycin C *Mitoxantrone*	Dry cold compress (3-day course)	*Topical DMSO 50–99%*
	Immediately for 20 min and four times daily	Immediately apply topically 1–2 mL with cotton swab over area twice the size of that affected and allow to air dry every 6–8 h for 7–14 days
Taxanes	Dry warm[a] compress (3-day course)	*Hyaluronidase*
Docetaxel Paclitaxel	Immediately for 20 min and four times daily	Inject 1–6 mL of 150 units/mL solution through the existing needle; if needle has been removed, inject 1 mL of solution per 1 mL of extravasated chemotherapy agent SC in a clockwise manner into multiple sites of the extravasation area using small-gauged (25 or less) needle; may repeat SC dose several times over the next 3–4 h
Vinca alkaloids		
Vincristine Vinblastine Vindesine Vinorelbine		

CrCl creatinine clearance, *DMSO* dimethyl sulfoxide, *IV* intravenous, *mg* milligrams, *SC* subcutaneous
[a]Some literature suggests using cold compresses with taxanes

ening injury at the extravasation site with warm compresses and rather recommends cold therapy to limit the diffusion of chemotherapy [135, 146, 147]. Pharmacologic treatment used for these agents helps dilute the offending agent (see Table 48.13 for dosing) [130, 140–144].

DNA-Binding Agents

Dexrazoxane

Dexrazoxane is approved for anthracycline extravasations. Dexrazoxane inhibits DNA topoisomerase II—the target of anthracyclines—minimizing pain and oxidative damage in the tissue by chelating metal ions from anthracycline [148]. Dexrazoxane is well tolerated and highly effective in avoiding surgical resection after anthracycline extravasation [140, 141]. Patients receiving dexrazoxane may experience bone marrow suppression (underlying disease and chemotherapy), mild transient elevation of liver enzymes (occurs in ~25% of patients), nausea (20%), and local infusion site pain [140]. Concomitant use with dimethyl sulfoxide may reduce the efficacy of dexrazoxane [149].

DMSO

Dimethyl sulfoxide (DMSO) is a topically applied solvent that increases skin permeability, promotes absorption of extravasated vesicants, and scavenges free radicals. DMSO has been studied in various amounts and concentrations (50–100%), application frequencies (every 2–8 h), durations of treatment (2–14 days), and for several different types of chemotherapy extravasations [137]. DMSO should be applied immediately and reapplied every 6–8 h for 7–14 days to decrease risk of ulceration and need for surgical debridement. Pain and erythema usually resolved in the first 1–2 weeks, and DMSO

may be used for up to 6 weeks. Reported side effects include mild pigmentation in the area, mild discomfort at the injection site, and a characteristic garlic breath odor [142]. Local DMSO in combination with dexrazoxane should be avoided. DMSO in combination may lessen the effects of dexrazoxane [135, 149]. Toxicity associated with mitomycin C may also be prevented by DMSO used topically [143, 150].

Sodium Thiosulfate

Mechlorethamine can cause severe ulceration and tissue damage. Sodium thiosulfate 1/6 M (0.17 M) solution is the only antidote currently available and recommended for extravasation of mechlorethamine or concentrated cisplatin (>20 mL of greater than 0.5 mg/mL) (see Table 48.13). When given subcutaneously into the extravasation area, sodium thiosulfate binds and neutralizes the extravasated vesicant and reduces production of hydroxyl radicals [151].

Non-DNA-Binding Agents

Hyaluronidase

Hyaluronidase can be used to treat vinca alkaloids or taxane extravasation [135, 144, 152]. Hyaluronidase is a protein enzyme that helps degrade hyaluronic acid that holds tissue planes together, rapidly dilutes the offending agent, and enhances drug absorption. Hyaluronidase doses range from 150 to 200 units, administered into the indwelling catheter or subcutaneously around the extravasation site [144, 149]. It has been shown to decrease pain and the amount of tissue injury over several days [144].

Surgical Intervention

The optimal timing of surgical intervention is unknown. Only one-third of vesicant extravasation in the extremities actually results in ulceration. Therefore, routine surgical intervention should not be the initial treatment [153]. Ulceration can progress to necrosis and infection. A plastic surgical consultation is recommended if the patient experiences a large-volume vesicant extravasation (not defined) and severe pain, if healing has not occurred 1–3 weeks after extravasation, or if there is early necrosis present [132, 135]. Surgical interventions may include debridement, fasciotomy, reconstruction, and grafting.

Saline flushing or washout/flush-out techniques have been described in the literature. There is some evidence that this may be beneficial. Several techniques have been used alone and in combination with other treatments [136]. The flush-out technique is usually performed by plastic surgeons, and the most recent described technique involves making several small-stab incisions and administering large volumes of 0.9% sodium chloride to dilute and flush out the extravasated drug [154, 155]. Saline washouts completed within 24 h of extravasation have been shown more effective than those completed more than 24 h post extravasation.

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Treatment Toxicity: Radiation

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Introduction

Exposure to radiation can result from diagnosis and primary management of a malignancy, or it can be an unintended consequence of nuclear accidents or an intentional act of terrorism. More than 60% of cancer patients will have radiation therapy as part of their primary treatment, and the accelerated risk of nuclear events increases our collective need for education of health-care providers in the knowledge and evaluation of radiation exposure and injury [1–8]. Although effects on tissue may not be visible or clinically apparent during an emergency evaluation, exposure is an important aspect to the medical history of the patient as it leaves an invisible clinical footprint which may be relevant to medical situations at a later time point, even decades after exposure. Intentional exposure is usually well documented with dose-volume precision in the radiation oncologic treatment record. However, at the time of an unanticipated emergency department visit, hospital record documentation is often limited to a few words describing treatment total dose and volume in a brief qualitative manner as the shadow radiation therapy record or radiation digital health record is often not directly linked to the hospital informatics systems. Therefore, information valuable to the emergency health-care team may be cursory, incomplete, or even inaccurate if obtained from a service unfamiliar with radiation treatment and exposure to normal tissue.

Unintentional exposure is more challenging to document and often limited to mathematical models of duration and distance from the primary incident, as victims are often unmonitored. While the models may be helpful, they often can be less accurate, especially in computation of the integral or total body dose [1, 6, 8]. Fluoroscopy during interventional radiology/cardiology procedures can lead to a surprisingly high-radiation dose to underlying structures that is often poorly documented, again comprising a relatively hidden risk in patient care [2–4].

With an increasing number of cancer survivors, including transition of survivors from pediatric to adult physicians, there is a developing knowledge gap at the primary care and emergency medicine levels concerning both acute and late effects of radiation exposure and how these interrelate with patient health care in the acute care setting. It is incumbent on the radiation oncologic community and radiation exposure experts to improve documentation and communication to health-care staff in order to better prepare patients and physicians for identifying contributing factors and strategies of short- and long-term normal tissue-driven processes that affect patients after radiation treatment and exposure.

Acute Radiation Toxicity: Unintended Exposure

Normal Tissue Toxicity

Acute toxicity from radiation exposure can be divided into acute (up to 90 days from exposure), subacute (from 90 days to 2 years from exposure), and chronic or late (>2 years from exposure) phases of injury. Although acute intentional injuries are traditionally managed by the responsible treating physicians during primary management of a malignancy, accelerated normal tissue damage that affects hydration balance and nutrition can often require evaluation by emergency services for triage and disposition. Unintentional exposure uniformly requires evaluation by emergency services with

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appropriate support from experts trained in managing acute radiation effects and radiation safety officers trained in assessing the nature of the exposure and possible radiation dose received by the victims. This would also include the evaluation of risk to personnel caring for the victim. The acute phase of injury can affect many cell systems, including toxicity to tissues of both limited and rapid self-renewal potential. These include, but are not limited to, the central nervous system, bone marrow, skin, and mucosal surfaces lining the head/neck and gastrointestinal system.

Knowledge of the effects of radiation damage to the body has been acquired through animal models as well as events in history documenting human exposure. These events include atomic bomb survivors and people affected through unintended nuclear fallout and nuclear accidents. Symptoms associated with unintended radiation exposure vary with the severity of the exposure. At very high single-fraction total body doses (>10 Gy), death will occur through cerebrovascular syndrome in spite of support within 24–48 h. The syndrome is due to uncontrollable swelling within the central nervous system associated with compromise of all neuromuscular processes. At total body doses of 5–12 Gy, death without support will occur in 1–2 weeks due to denudation and destruction of the gastrointestinal system associated with profound fluid loss and diarrhea. These cells have a self-renewal capacity measured within a few days; thus, a single total body dose of 10 Gy will eliminate a large portion of the stem cells within the gastrointestinal crypts. Although this dose does not affect differentiated adult cells, the exposure eliminates the self-renewal potential of the stem cell; therefore, the mucosal surface of the gastrointestinal tract becomes denuded with no barrier for fluid and blood loss within a short period of time, measured in days. At total body exposure doses of 2–5 Gy, death will occur from damage to the hematopoietic system with primary damage to progenitor cells inhibiting self-renewal. Lymphocytes may die an intermitotic death, and this finding may be a surrogate biomarker for acute exposure within the first few hours to days of an incident [1, 5–8]. However, by day 30, most circulating blood elements are depleted with death often attributed to infection. The term, LD (lethal dose) 50/30, is borrowed from our pharmacology colleagues and reflects the LD of an agent that will cause 50% mortality in 30 days. Although radiation is not a drug, the LD 50/30 is now generally thought to be 5 Gy with modern hospital support [1].

After exposure, victims will develop symptoms consistent with a radiation syndrome that can be visible as early as 15 minutes from the time of exposure [1, 6, 8]. The reaction may last several days until symptoms merge with other events associated with the exposure. Symptoms are generally gastrointestinal and neuromuscular. At lower doses, victims experience anorexia, nausea, and vomiting associated with lassitude. The degree of symptoms is commensurate with dose. At higher doses, patients can experience severe diarrhea, fever, and hypotension suggesting more immediate toxicity including more pronounced neural damage. Usually at low doses, the prodromal phase is followed by a latent period where the victim may appear and feel well for a period of days to weeks. At that point gastrointestinal and hematopoietic damage becomes more evident and requires intervention [1, 5, 6, 8].

If the total body exposure is less than 4–5 Gy, the majority of experts recommend no immediate intervention other than symptomatic treatment as needed. This would include hydration and antiemetic therapy for nausea/vomiting. Antibiotics can be given for infection as needed. If the exposure is greater than 5 Gy, then death associated with the hematopoietic syndrome becomes a real concern. Intervention with isolation and barrier nursing with appropriate blood product support may improve survival. Experience from Chernobyl suggests that efforts to limit infection, bleeding, and physical trauma during the time of blood count nadir may improve the LD 50/30 to and possibly beyond 7 Gy. To the best of current knowledge, no human being has survived a single total body exposure beyond 10 Gy. The use of bone marrow transplant in this setting remains controversial with strong advocates on both sides of the question [7].

Injuries to the gastrointestinal system and hematopoietic systems may be accompanied by dermal injury. Often in particle exposure including low-energy photons, there is significant asymmetry in dose as often the event is triggered by an accident involving the hands. Dermal injuries can be primitive biomarkers for dose with epilation/erythema at doses of 3–6 Gy and wet desquamation, bullae, ulceration, and necrosis seen at higher doses [1, 9]. These injuries can be life-threatening due in part to concomitant infection and should be managed with the same support offered to burn victims.

In the triage of victims with unintended exposure, it is most important to develop as accurate an assessment of dose as possible. Health-care workers will likely be monitored; however, the general public will not, and therefore experts trained in radiation exposure and dose assessment are crucial in the early phase of the evaluation. There are several basic tools to use as part of the initial evaluation. The time to emesis decreases with increasing radiation dose. The rapid onset of nausea and vomiting suggests a higher exposure. A decline in lymphocyte count can be associated with an exposure dose of best relative estimate occurring within 48 h of exposure. This is often hampered because the preexposure lymphocyte count is unknown. If a laboratory for cytogenetic evaluation is available, another surrogate evaluation is to assess the number of chromosomal aberrations in peripheral lymphocytes when they are stimulated to divide. This technique has more value at lower doses as lymphocytes die quickly at high doses [1, 7, 8].

There have been numerous nuclear accidents over the past 50 years with people exposed to total body or partial body radiation. These include nuclear events as well as unintentional exposure to victims unaware of the immediate risk [6, 8]. The Medical Sciences Division of the Oak Ridge Institute for Science and Education operates a Radiation Emergency Assistance Center for the US Department of Energy. The center is a 24-h consultation service with medical and health physics support for issues associated with radiation events and exposure. Resources include expertise for radiation dose assessment, computation of dose from radionucleotides, and laboratory facilities for dose assessment. The 24-h emergency telephone number is 865.576.3131, and the website is http://www.orau.gov/reacts.

Since the development of nuclear weapons, there has been a keen scientific interest in identifying chemical compounds that can protect normal tissues from the effects of radiation exposure. Radiation protectors are elements that are given prior to exposure or in some cases, shortly thereafter, to limit the effect of exposure on normal tissue. Radiation mitigators are compounds that have the potential of influencing the effect and impact of the exposure. Therapeutic compounds are applied once the injury has occurred. There have been more than 4000 compounds synthesized to address this point. Sulfhydryl compounds (SHs) have been shown to be effective radioprotectors with the simplest compound being cysteine, which contains a natural amino acid. It was shown in 1949 that this compound could protect animals from lethal doses of total body radiation if injected or injected in large amounts (equivalent of 150 mg/kg) [10, 11]. The toxicity of sulfhydryl compounds can be limited by the addition of a phosphate group [10]. Once the compound becomes intracellular, it loses the phosphate group, and the compound is thought to serve as a free radical scavenger limiting intracellular damage. The only compound approved by the US Food and Drug Administration (FDA) is amifostine (WR-2721). It is sold as Ethyol and has been used to prevent xerostomia in patients undergoing radiation therapy for head/neck carcinoma [12]. Amifostine has been used in several clinical trials evaluating effectiveness in protecting multiple mucosal surfaces as well as a protectant for pulmonary injury in patients undergoing total body radiation therapy as part of bone marrow transplant [12]. In a Radiation Therapy Oncologic Group (RTOG) clinical trial, amifostine was associated with an improvement in patient assessment of mouth dryness and swallowing [12, 13]. In this trial, there was no difference in tumor control between patients receiving amifostine or placebo. Citrin and colleagues [10] have identified nitroxides as agents for radioprotection in clinical development. Stable nitroxide free radicals and their specific electron reduction products, hydroxylamines, protect cells when exposed to oxidative stress; therefore, compounds such as these are under evaluation. Other antioxidants, including alpha-tocopherol and beta-carotene, have not yet been shown to be of clinical benefit [14, 15]. Simultaneous tumor protection has been a concern in the clinical use of radioprotectors and is the reason these compounds have not been easily integrated into clinical management. Investigators have explored the use of intracellular superoxide dismutase (SOD) using gene therapy vectors to enhance the intracellular component of SOD to limit damage caused by superoxide radicals [16, 17].

Mitigators are compounds that can limit damage associated with radiation exposure prior to the clinical manifestation of both acute and late toxicities of radiation exposure and treatment. These compounds are generally thought to influence the metabolic cascade of events that occur after exposure and in turn limit radiation-associated damage. To date, most of the compounds are cytokines and growth factors directed to stimulate stem cell proliferation and balance the inhibition of stem cell growth induced by radiation to the hematopoietic and GI systems. These include granulocyte colony-stimulating factor (G-CSF) and keratinocyte growth factor (KGF) [18]. These factors contribute to many aspects of cell recovery. KGF has a positive influence in the recovery of mucosal surfaces during the acute phase of toxicity as well as limits the late effects of radiotherapy, including xerostomia [10]. Mitigators of late toxicity are largely directed to limit fibrosis, which is thought to be a primary factor in late pulmonary injury and other tissues of more limited self-renewal potential [10, 14–17, 19–23]. The primary target for this strategy is thought to be transforming growth factor beta (TGF B), which appears to play an important role in the development of fibrosis associated with radiation [24–26]. Accordingly, many compounds in development to prevent late effects either directly or indirectly target the TGF B signaling pathway including receptor inhibition [24–26]. Tumor protection is also a concern in the evaluation of treatments associated with this parallel pathway.

Investigators at the University of Massachusetts Medical School have evaluated the use of interleukin-1 alpha (IL-1α) as a mitigator to dermal damage associated with radiation exposure. Interleukin-1 (IL-1) inhibits neutrophil infiltration into the initial inflammatory response to radiation damage. Dermal injury was induced with electron particle therapy. Knockout mice deficient in IL-1α or the IL-1 receptor demonstrated both decreased dermal injury and more rapid healing suggesting the importance of this cytokine in the generation of radiation-associated skin damage. Neutrophil inhibition generated subsequent to radiation-induced tissue injury influences the pathogenesis of radiodermatitis. In a separate group of experiments, investigators from the same institution demonstrated that hyperspectral optical imaging (HSI) can demonstrate both acute and late oxygenation and perfusion changes in dermal tissue with changes occurring as early as 12 h after radiation exposure using a strontium-90

applicator [27, 28]. Imaging changes in oxygenation and perfusion predated clinical visible skin change by 14 days [28]. Unpublished data sets from this group as part of a human IRB clinical trial in breast cancer patients undergoing radiation therapy have shown that changes in imaging correlate very well with radiation dose and dose asymmetry in the treated volume.

In summary, with the increased risk of nuclear radioterrorism and increased radiation exposure identified during air and space travel, there is a renewed sense of urgency to better define and refine our response to a nuclear event. It is important to acknowledge that dose and particle contamination become essential points during the initial triage of the patient. Potential exposure to first responders must be assessed. The best supportive care has the potential of improving patient survival, which may include hydration and blood product support. There is renewed interest in developing a targeted pharmacologic response to both protect and mitigate issues surrounding radiation exposure [29].

Normal Tissue Effects of Radiation Therapy

Often oncologic patients under active treatment are seen in evaluation by emergency physicians, particularly during non-primary clinic times including evenings and weekends. In large academic centers, this practice is under change as outpatient weekend service is becoming more important to clinical oncologic as more primary patient care management, including bone marrow transplantation, moves to the outpatient setting. Nevertheless, often emergency personnel are involved with patient care matters that are directly or indirectly associated with the management of the malignancy or the sequelae of management including triage of acute care problems that may be related in part to previous therapy delivered years and decades in the past. In the following sections, we will address sequelae of management and how this influences patient care for modern emergency medicine [30].

Management of Acute Effects of Radiation Therapy

Sequelae to normal tissue are mostly attributed to cell death from radiation therapy. The balance between stem cell development and cell death is driven in a large part by tissue organization, stem cell proliferation, stem cell number, and cytokine response for growth stimulus. Acute effects from therapeutic radiation therapy are associated with cell systems that have rapid self-renewal potential including bone marrow progenitors and mucosal surfaces. These sequelae are driven by several factors including the concomitant use of cytotoxic chemotherapy and the volume of mucosal tissue in the radiation therapy treatment field. Acute effects generally occur during the course of radiation therapy and can affect multiple organ systems largely associated with mucosal surfaces including the skin, head/neck, gastrointestinal tract, and bone marrow. Acute effects are exacerbated by the use of chemotherapeutic and/or molecularly targeted small molecule agents delivered both before and during radiation therapy. Although not well validated through mechanism, patients can experience dramatic acute effects from low-dose radiation therapy to the skin and mucosa if they have received prior sensitizing medications including low-dose chemotherapy for autoimmune disease (methotrexate for rheumatoid arthritis) and selected antibiotics (tetracycline) [9]. The phenomenon, referred to as radiation recall, can even be seen in patients who received medications years in the past [9]. Although acute effects mostly impact tissues of rapid self-renewal potential, there can be selected circumstances where near-immediate changes occur that are often not anticipated by the primary providers of care. Patients treated in the head and neck region can experience swelling of the parotid glands with 24 h of exposure of 200 cGy. The adventitia of the parotid gland is tight with limited capacity for expansion from swelling; therefore, rare patients can experience severe pain and discomfort from low-dose therapy. There is often a need to urgently treat patients with significant tumor burdens, particularly in the mediastinum. Radiation to tumors of the mediastinum particularly sensitive to treatment (lymphoma, small cell lung cancer, or germ cell neoplasm) can trigger both nausea and metabolic crisis (hyperkalemia, hypercalcemia, etc.) from rapid tumor lysis. Symptomatic treatment including fluids and medication to counter metabolic by-products is essential for a good outcome.

Acute effects to tissues of rapid self-renewal potential are influenced by total radiation dose, daily treatment dose (fractionation), and volume of tissue treated. This information is often not immediately available to emergency departments when patients present for evaluation as specific treatment documentation is often in the department shadow record and not directly integrated into electronic health-care records. The volume of the treatment target influences the number of stem cells directly affected from daily treatment. Daily treatment dose also influences injury to stem cells. Hence, total and daily doses as well as target volume are all directly related to the development of sequelae from the treatment. Specific acute injuries to organ systems are discussed in the following section.

Skin

The epidermis is the site of many acute reactions to radiation exposure. The dermal stem cells abut the basement membrane and are the active proliferating cell component covered by lay-

ers of keratinized cells, which are desquamated. The stem cells are the target for injury. The time for dermal cell division and migration is between 14 and 21 days depending on the area of the body under evaluation. Single doses of 5 Gy will generate early erythema followed by vasodilation, fluid exudation, cellular migration, and loss of proteins and other constituents of plasma products [9, 31, 32]. Investigators have shown that this process can be identified on hyperspectral imaging within 12 h of exposure with evidence that the evaluation on imaging can be dose specific in spite of the fact that clinical expression of change may not become apparent for 2–3 weeks [27, 28]. Fluoroscopy procedures use orthovoltage (low-energy) X-rays that deliver higher percentages of radiation dose to the skin surface [2, 3]. Complicated procedures in interventional radiology requiring significant fluoroscopy time can create acute dermal injury even in the modern era as acute injuries are influenced by fractionation (daily dose) and total dose. With hypofractionation protocols using high daily dose with compressed treatment schedules including stereotactic therapy for the lung and liver, we are again witnessing injuries to the skin and soft tissue that were traditionally seen in a historical context [33]. The treatment for acute injury is driven in a large part by radiation dose and treatment volume. Modern accelerators deliver the majority of the radiation dose below the skin surface; therefore, with traditional fractionation, it is unusual to have patients demonstrate significant dermal sequela with conservative measures, including various skin creams and ointments. Radiation beams resonate on skin surfaces within dermal folds; therefore, these intertriginous areas are more vulnerable to injury during treatment. Hypofractionation protocols may deliver a higher-dose fractionation to dermal surfaces if treatment planning is not optimal. There are reported soft tissue injuries to the skin during stereotactic body radiosurgery when immobilization devices unintentionally functioned as bolus devices augmenting radiation dose to skin surfaces [33]. As information matures on molecularly targeted therapies, there is increasing evidence of skin toxicity to multiple new agents including EGFR inhibitors (rash 2–4 weeks into therapy), BRAF inhibitors (rash/photosensitivity), BCR-ABL inhibitors (keratosis pilaris/maculopapular rash), and m-TOR inhibitors (rash/pruritus) [10].

Hematopoietic System

The effects on the hematopoietic system are driven by the volume of the bone marrow and lymphoid system treated, previous chemotherapy and radiation treatment, as well as radiation dose. Age of the patient also influences bone marrow injury as there is asymmetry of location in marrow locations between children and adults. Total body exposure will result in a near-immediate decrease in circulating B and T lymphocytes, and a total body dose of 3.0–4.0 Gy likely inhibits the ability to respond to new antigen stimuli. Most patients receive radiation treatment to a partial body, and usually partial organ volume that would have a limited effect on the immune response unless the patient is neutropenic from concurrent chemotherapy [34]. This permits migration of stem cells from outside of the therapy field to stabilize bone marrow function.

Gastrointestinal Tract

The mucosa of the tract has similar organization to skin tissues as stem cells reside at the basal layer and migrate to the surface at varied time points during their life cycle. In general, the cells that line segments of the gastrointestinal (GI) tract possess a shorter life span than their counterparts in the skin. The mucosa of the head and neck and large bowel self-renew every 2 weeks, the mucosa of the gastric region renews nearly every day, and the small intestine renews every 3 days. This explains, in part, why nausea from therapy directed to the gastric region and small bowel can be apparent very early postexposure.

Because the mucosal systems have rapid self-renewal potential, acute sequela from management can be substantial and is driven by radiation dose, daily treatment fraction, and volume of mucosa in the treatment field. By the second week of treatment, the mucosa of the head and neck becomes denuded with increasing pain. Secondary tissues including salivary glands and taste buds also display limited function driven in a large part by the volume of mucosa in the treatment field. By week 4, the mucosa will slough and be replaced by confluence of white cells and fibrin exudate. The impact on secondary tissues becomes more pronounced with severe xerostomia and loss of taste. This creates challenges with maintaining adequate dental hygiene and nutrition. Often patients treated to substantial mucosal volumes require supplemental nutrition for extended periods of time during and beyond treatment completion. These patients can be cured of their primary malignancy; therefore, adopting an aggressive approach to the management of the acute effects from the treatment is reasonable and medically appropriate. Symptomatic pain management with topical and enteral medications is an important management vehicle for care during this period of time [34].

The epidemiology of carcinoma of the esophagus has changed during the past 30 years in North America. Squamous cell carcinomas associated with alcohol and tobacco use have been replaced by primary adenocarcinomas, largely of the distal esophagus associated with gastric surface gland migration (Barrett's esophagus). This has been seen in multiple countries and is now the great majority of esophageal cancers. The mucosa of the esophagus will self-renew in a time frame similar to head and neck mucosa; therefore, 2 weeks into a treatment course, the patient will

begin to develop swallowing discomfort related to treatment. Often these patients initially feel improved due to tumor response; however, mucosal denudation from treatment also becomes apparent during this time, and symptoms associated with dehydration and nutritional imbalance become more visible. Symptomatic management with pain medication and fluid support is an important adjunct during this period.

Treatment of the gastric mucosa can cause near-immediate nausea/vomiting due in a large part to the rapid self-renewal capacity of gastric stem cells. During a treatment course of radiation therapy, delayed gastric emptying can be observed due to edema in the bowel wall as well as the development of ulceration due to limited stem cell renewal capacity.

Early complications of the small and large bowel are similarly driven by radiation dose, treatment fractionation, volumes of bowel in the radiation therapy treatment field, and previous abdominal surgery. Previous abdominal surgery can result in adhesions which can fix segments of the bowel into a specific location, potentially exacerbating acute injury due to limitation of blood supply and repeated high-dose treatment [15, 35]. The small bowel absorbs protein, carbohydrate, fat, and water. If the mucosal surface is denuded, foodstuffs cannot be absorbed. Carbohydrate and fat function as a micelle and draw more water into the gastrointestinal tract resulting in increased bowel movement frequency and symptoms consistent with malabsorption. The large bowel mainly absorbs water; therefore, if generous segments of the large bowel are included in the therapy field, increased bowel frequency may occur with risk of dehydration and electrolyte loss often exacerbated with the concurrent chemotherapy. Although some of these issues can be anticipated and addressed through daily clinical care with fluid and electrolytes, often, these patients present for emergency department evaluation during evenings and weekends for symptom management. Therefore, up-to-date clinical information can often facilitate and support emergency services when needed including the risk of secondary infections associated with therapy. From a clinical perspective, patients being treated for recurrent disease often have more acute and potentially more serious sequela than patients being treated on an adjuvant basis. The root cause for this phenomenon is multifactorial, likely driven in part by tumor compromise of normal tissue function and vasculature prior to the initiation of therapy [34].

Subacute and Late (Delayed) Effects of Treatment

For both primary and emergency health-care providers, the late effects of cancer management can be less visible to casual observation but become a highly visible component to patient care years and decades after primary management. As patients are cured of their primary malignancy, secondary effects of therapy on normal tissue structure and function are now important for follow-up and preventative care as needed. As children treated for malignancy grow and become adults, adult physicians will need to embrace previous therapy as a significant component to their past medical history and treat accordingly. Acute effects of treatment are not always a predictive indicator of late effects, specifically patients without acute effects during the primary management phase of treatment remain at identifiable risk for late effects.

Usually acute effects of radiation management affect cells that have a rapid self-renewal capacity. Nearly every cell system in both adults and children is at risk for late effects driven in a large part by the total radiation dose and volume of normal tissue treated. Late effects are also influenced by daily treatment dose. Children remain at significant lifetime risk as growth and development of all cell systems is directly affected by therapy [15].

The relationship of chemotherapy to delayed effects from radiation therapy to normal tissue is less well described [15]. Although it is recognized in a qualitative manner that chemotherapy exacerbates acute effects of radiation therapy to tissues of rapid self-renewal potential, the impact of chemotherapy on late effects of treatment is not understood. To date, most radiation oncologists have not made adjustments in dose to normal tissue targets; however, our volumetric dose volume tools are now providing metrics through histogram analysis. The quantitative analysis of normal tissue effects in the clinic (QUANTEC) is a significant effort by radiation oncologists to define dose volumetrics for thresholds for normal tissue injury [36]. This effort reviewed most of the available and relevant published data to date and provides guidelines for physicians to follow for prevention of injury [36]. Because of modern computer metrics, the guidelines are driven by radiation dose and volume exposed to treatment. When treatment is developed through three-dimensional planning and executed through conformal delivery systems, including intensity modulation, normal tissue volumetrics are available for analysis through dose-volume histogram tools.

In this section, the late effects of radiotherapy will be described. This is important for emergency physicians as often this information is not available as part of the past medical history of the patient during an acute care evaluation and triage for advanced medical care. Improved knowledge of late effects will influence management and evaluation including the evaluation strategy in the acute care setting. Understanding these effects will improve patient care and evaluation moving forward.

Skin

Acute effects (described previously) of radiation injury to the skin generally resolve within 1 month of completion of

therapy. With traditional fractionation to radiation doses of 7000 cGy, there can be thinning of the epidermis with deceptive prominence of the vascular pattern (telangiectasia) in the dermis. The degree of vascularity is decreased; however, thinning of the epidermis can make the vessels in the dermis appear more prominent [9]. With hypofractionation protocols now in clinical use, there can be more visible injury associated with varying degrees of fibrosis [33]. Hyperspectral imaging demonstrates that oxygenation is decreased, providing an explanation to limitations in wound healing when there are secondary injury and infection [10, 27]. Local immunity and moisture glands significantly diminish; therefore, injury to irradiated tissue can result in significant delay in healing with persistent ulceration and damage possibly requiring aggressive surgical care including hyperbaric oxygen therapy in extreme situations [9]. To date there has been little progress on specific therapies that can be applied to radiation injury once it is clinically apparent. The current standard of care is to follow optimal wound care strategies.

Skin tissue can also demonstrate a phenomenon termed *recall*. Chemotherapy agents and antibiotic agents can cause acute erythema and skin breakdown in areas that were previously irradiated. This can occur years after primary radiation therapy management.

Patients with autoimmune disorders including lupus and scleroderma may be vulnerable to accelerated fibrosis from traditional radiation therapy. This creates wound healing issues for secondary injury as well as limitations in function of organs requiring coordinated muscle function including the esophagus [9].

The mechanism of visible injury is due to damage to stem cells and the reticulum support elements of the skin. The repair becomes disorganized, and the injury to the dermis does not support the development of the epidermis as in an untreated skin. Secondary infections are more difficult to heal when identified in treated areas.

Bone Marrow

Although the primary focus of attention is with acute effects, the bone marrow can remain fragile years after therapy and vulnerable to various medications and external agents after radiation therapy. This is especially true for white cell elements and platelets. If there is a diminution in red cell count, this is usually not associated directly with radiation therapy and will require more extended evaluation for blood loss and anemia. Pancytopenia and bone marrow aplasia are becoming more common consequences of cancer therapy and often first identified in an acute care environment. This often influences choice and duration of treatment of infections and other late sequelae of management. Secondary blood dyscrasias including secondary blood malignancies are associated with primary management and are often first identified in the acute care setting [15, 34]. The role of transplant of both primary and support cell marrow elements to repopulate bone marrow remains under study.

Gastrointestinal Tract

There are substantial late effects of management to be considered in the acute care environment. These are issues that can significantly complicate patient management and often require adjustments in management.

The mucosa of the oral cavity recovers in a manner similar to the skin; however, there is residual compromise of the oral cavity environment, which is long-standing in nature. The floor of the mouth is taut and lacks mucosal redundancy; therefore, it is susceptible to injury and heals less well than other structures in the oral cavity. If ulceration occurs, debris and particles can sequester in the open space and cause necrosis of underlying structures including the mandible. This requires careful management including hyperbaric therapy and surgery. These issues are challenging and may become more frequent as radiation therapy moves to more hypofractionation protocols for head and neck cancer. Patients have dry mouth due to radiation dose to the parotid glands, the submandibular glands, and the often overlooked submucosal gland structures that provide moisture to the mucosal surface. These microscopic glands are ubiquitous in distribution throughout the mucosal surface and create secondary issues for dentition in adults and children. Although teeth do not self-renew and by default are not directly affected by radiation, treatment affects the oral cavity environment and both the growth and development of teeth in children and the oral cavity environment for adults. The saliva becomes more acidic and prone to fungal overgrowth. The gingival mucosa becomes thin and denuded. These changes can lead to chronic decay and demineralization of teeth. Fluoride mouthwash with periodic use of baking soda/water rinses helps deacidify the oral cavity and promotes more optimal oral hygiene; however, these changes are often unrelenting and difficult to control. Optimal radiation planning strategies with intensity modulation may help mitigate these changes moving forward. Building a strong relationship with dental medicine helps facilitate optimal patient care [15, 34].

Motility of the gastrointestinal tract is not a well-described side effect of radiation management; however, this is becoming a more visible issue in the management of head and neck malignancies and esophageal cancers [37]. Contractility of the medial constrictor muscles of the hypopharynx is now described and appears to mimic swallowing issues often seen in patients with neurodegenerative disorders [37]. At times these changes are related to treatment-associated dermal and

interstitial edema, and addressing the edema through lymphedema clinics can be very helpful. As more patients survive their primary malignancy, these issues are becoming more frequent and impose significant restrictions on patient recovery from treatment. Delayed gastrointestinal emptying associated with antral fibrosis and denudement of the mucosa of the gastric lining cells can be seen in patients treated to the gastric region, usually at doses of greater than 45 Gy to the gastric region or the gastric resection site.

Late effects to both small and large bowel include every tissue component. There is atrophy of the mucosa resulting in limited absorption of protein, carbohydrate, and fat. This contributes to various degrees of malabsorption syndromes and inconsistent bowel function. If there is previous abdominal surgery, the bowel may be fixed in position resulting in stenosis and ulceration requiring surgery. Relatively little is known about effects to the exocrine and endocrine pancreas although atrophy of the pancreas can be seen on imaging years after treatment of an upper abdominal malignancy [15, 34].

Liver

There is renewed interest in defining radiation dose effects to the liver as stereotactic body radiosurgery techniques have been effective in the treatment of both metastatic disease to the liver and primary hepatocellular carcinoma. Sequela to the liver, known as radiation-induced liver disease (RILD), is driven by the volume of the liver treated and the functional status of the liver at the time of therapy. Both primary and metastatic diseases can impose varying degrees of veno-occlusive changes in the parenchyma, and treatment can induce scar tissue that can limit the functional status of the remaining liver. Magnetic resonance imaging has become a valuable tool in validating the degree of veno-occlusive changes and has evolved into a quantitative metric in predicting possible radiation-associated liver injury prior to the administration of radiation therapy [38]. Investigators are using metrics identified on dynamic contrast imaging to establish the appropriate radiation dose to target. The threshold of injury to the liver is significantly decreased when the entire organ volume is treated. Sioshansi et al. have demonstrated injury to the diaphragm without changes in the chest wall resulting in chronic pleuritic pain among patients undergoing stereotactic body radiosurgery [39]. The liver is sensitive to interactions with chemotherapy perhaps best demonstrated in the pediatric population when radiation therapy is delivered with actinomycin D chemotherapy for Wilms' tumor. Sequela can include a dramatic decrease in blood counts as well as changes consistent with liver failure including coagulation disorders [34].

The mechanism associated with therapy-associated hepatic injury is related to direct injury to hepatocytes and the structural integrity of their organization. The injury is expressed through the associated disorderly repair of hepatocytes coupled with nodular regeneration limiting normal function of the liver. Investigators are currently describing two forms of radiation-induced liver disease. The traditional form of injury (classical) is imposed on pre-injury normal hepatic parenchyma. In these patients, abdominal pain, hepatomegaly, anicteric ascites, and elevation of alkaline phosphatase are seen as the clinical manifestation of injury. In nontraditional (nonclassical) injury, patients often present with jaundice and elevation in transaminase enzymes. Biopsy of the liver will demonstrate edema of the endothelium and narrowing of hepatic venules creating retrograde congestion and veno-occlusive changes. Microthrombi can develop which further exacerbates congestion. Models have demonstrated that an increase in transforming growth factor beta is associated with increasing degree of injury. Hepatic stellate cells are responsible for regeneration of hepatocytes as well as secretion of various growth factors supporting development and regeneration. However, if the reticulum architecture is damaged, the hepatocytes do not have an infrastructure platform to repair in an orderly manner. Disorganized repair is nodule regeneration. Because of a larger separation between hepatic parenchyma and the blood supply, the liver has less meaningful function. This is reflected in the fact that radiation-induced liver disease has a lower threshold for injury when therapy is applied to the liver with pre-existing injury prior to radiation therapy. It is thought that the mean dose threshold for injury in the otherwise healthy liver is 30 Gy while the mean dose threshold for patients with pre-existing injury or lower based on the degree of pre-existing comorbidity.

Because there are no identified therapies to mitigate or treat injury, prevention of injury is essential for current cancer management. Modern radiation therapy techniques including image guidance and motion management have significantly improved patient care and limited the impact of therapy on normal tissue function. Modern imaging techniques including indocyanine retention and magnetic resonance imaging have served as excellent surrogates for liver function which have supported appropriate targeting and radiation target dose and dose fractionation [38, 40–42].

Kidney

The kidney, similar to the liver, is a relatively late-responding radiosensitive critical organ. Radiation doses of greater than 20 Gy in 2 Gy fractions can result in renal damage with anemia and hypertension. Although not yet validated through clinical trials, the threshold for injury is thought to be lower when nephrotoxic chemotherapy is used with radiation therapy. Using intensity modulation and image guidance, radiation

oncologists can be creative with partial volume therapy and spare as much renal parenchyma as possible. Nevertheless, in comparison with siblings, there is an increased risk of renal failure in the cancer survivor; therefore, investigators should attempt to limit renal dose to as little as possible during treatment planning. To date this issue has not yet been defined as a point of interest for imaging and avoiding delivery of contrast agents; however, this may become an important issue in the clinic moving forward [15, 34, 36].

The mechanism of injury is multifactorial as radiation therapy likely has impact in all compartments of the kidney including the glomeruli, mesangium, and endothelium. Often injury from therapy is challenging to distinguish from more typical forms of injury including hypertensive renal disease. Oxygen-related species generated as secondary byproducts of therapy are thought to directly impact glomeruli with denuded tubules permitting entry of toxins into interstitial tissues. The development of scar within the kidney and subsequent decrease in size of the affected area are thought to be driven in part by transforming growth factor beta. The sequelae of injury include hypertension which needs to be managed aggressively and followed with rigor. Often the use of angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers is helpful in management. As per other sites of normal tissue injury as noted, the best therapy is prevention. Care and attention to radiation therapy treatment planning with intentional conformal avoidance of renal parenchyma during therapy is essential for the modern cancer patient [43–45].

Lung

As with the liver and kidney, the lung is a very sensitive intermediate to a late-responding tissue. In extreme situations, injury to the therapeutic lung can be life-threatening. There are generally two periods of damage that can be identified. Pneumonitis (period of active inflammation) can occur 2–6 months after completion of radiation therapy, and fibrosis can occur years after treatment delivery. During the pneumonitis phase of injury, there is active inflammation often visible on thoracic imaging. If the patient is asymptomatic, observation is a reasonable approach. Symptoms including cough and shortness of breath associated with these imaged changes are often managed by corticosteroids and antibiotics as appropriate [46]. There are reports of radiation injury to the lung tissue outside of the radiation treatment field. Although felt to be spurious at initial review, investigators have suggested that production of nitric oxide gas as a byproduct of radiation-induced injury may play a role in generating injury in other parts of pulmonary parenchyma not directly in the radiation therapy treatment region [47]. Fibrosis as a late change can result in parenchymal scar as well as pleural and pericardial effusions resulting in limitation of pulmonary reserve and chronic need for supplemental oxygen. Modern radiation techniques including the use of motion management and intensity modulation may limit the risk of injury by limiting the volume of parenchyma receiving higher doses. Dose-volume histogram analysis also suggests that it is likewise important to limit the volume of normal lung parenchyma receiving 20 Gy. Modern radiation therapy techniques seek to limit the volume of lung receiving both high and low doses. Interactions with other pulmonary toxic agents such as bleomycin play a key role in evaluating the dose-volume effect of radiation therapy. This is especially important in patients treated for Hodgkin lymphoma. Recent studies do reveal an increased risk of chronic pulmonary disease in cancer survivors in comparison with siblings [15, 24, 25, 48].

The mechanism of pulmonary injury is directly related to damage to lung parenchyma. Radiation both primarily generates injury and secondarily creates reactive oxygen and nitrogen species that produce oxidative injury to cell structures leading to cell death. Predominantly, type 1 pneumocytes are directly injured by radiation. Type 2 pneumocytes are less common. Although they can de-differentiate into type 1 pneumocytes, they are conversely stimulated by radiation and exhibit hyperplasia and growth following exposure. Hyperplasia is associated with growth factor production including removal of debris. Inflammatory cells migrate into the region which leads to fibroblast production and fibrosis. Initially the injury is related to cell death and damage to alveolar/capillary structures which ultimately lead to disorganized repair and fibrotic lung tissue.

The degree and severity of injury are often driven in large part by the volume of parenchyma treated. Other variables influencing outcome include baseline pulmonary function and medical comorbidities. Chemotherapy including immunotherapy can have a significant influence on outcome including patients who have favorable metrics with respect to radiation therapy treatment volumes. Radiation metrics including volumes of regions receiving high, moderate (V20, volume receiving 20 Gy), and low (V50, volume receiving 5 Gy) dose each contribute to a normal tissue outcome with varying degrees of influence, often in a patient-specific manner. Further research is needed to see how these variables relate to each other as predictive indicators of function and outcome [49–51].

Case Study

Two patients in Figs. 49.1 *and* 49.2 *represent therapy-driven pneumonitis outlining the radiation therapy field while on immune checkpoint inhibition with improvement after withdrawal of the drug.*

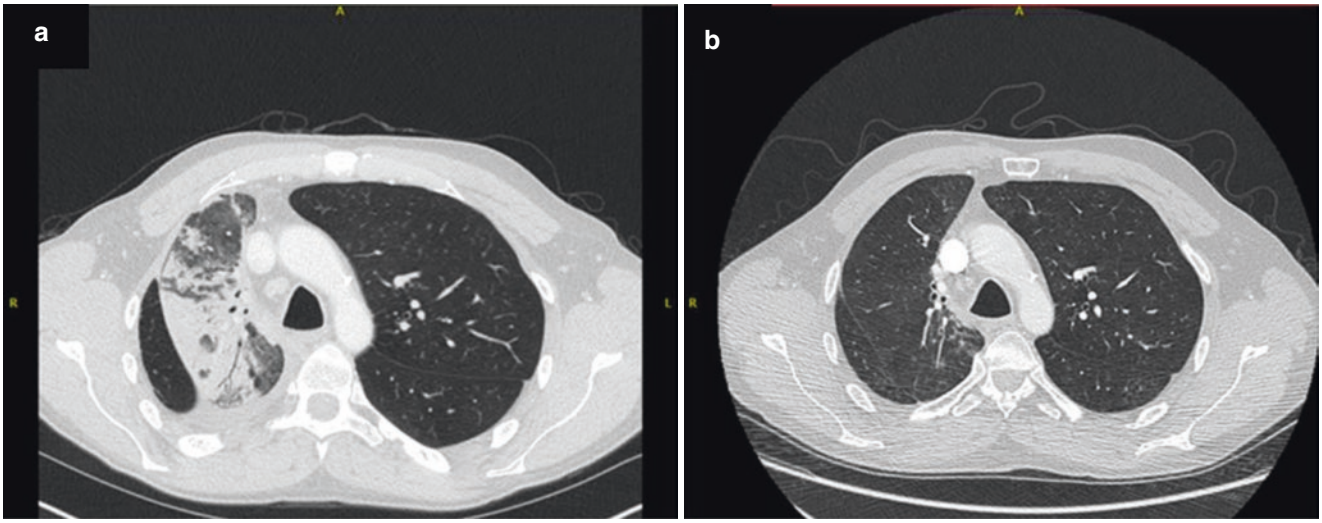

Fig. 49.1 Case study. Patient 1. Therapy-driven pneumonitis outlining the radiation therapy field while on immune checkpoint inhibition with improvement after withdrawal of the drug. (**a**) Before immunotherapy withdrawal. (**b**) After immunotherapy withdrawal. (Courtesy of the Department of Radiation Oncologic, University of Massachusetts Medical School, Worcester MA)

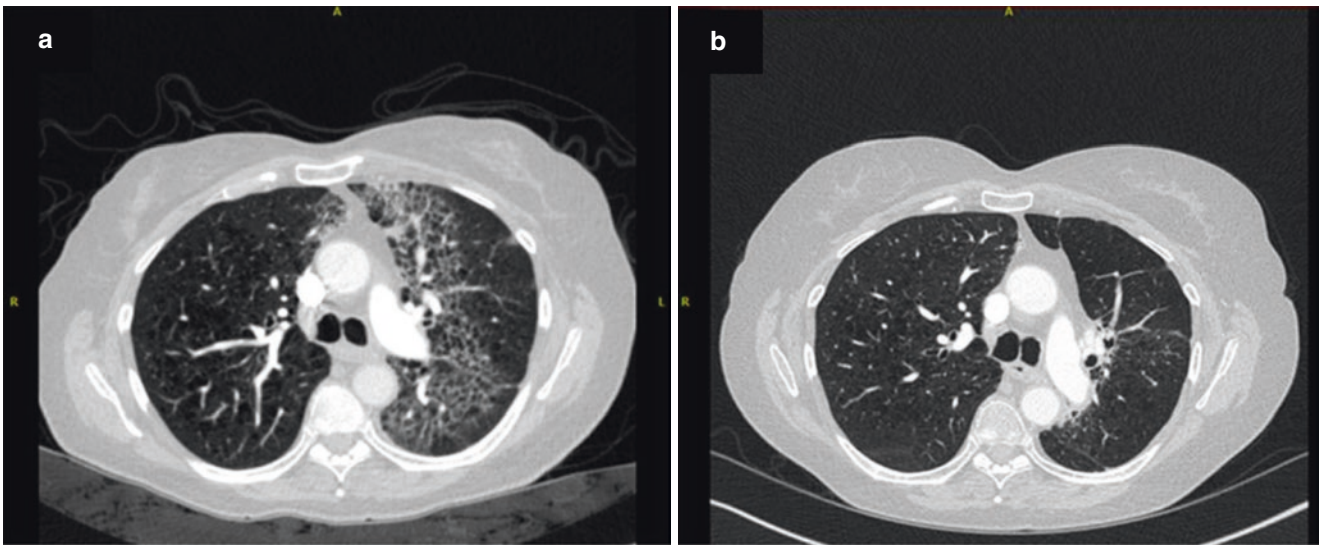

Fig. 49.2 Case study. Patient 2. Therapy-driven pneumonitis outlining the radiation therapy field while on immune checkpoint inhibition with improvement after withdrawal of the drug. (**a**) Before immunotherapy withdrawal. (**b**) After immunotherapy withdrawal. (Courtesy of the Department of Radiation Oncologic, University of Massachusetts Medical School, Worcester MA)

Heart and Peripheral Vessel

Historically the heart was considered to be a late-responding tissue with exception of pericarditis, which could occur during or shortly following radiation therapy, especially in patients with generous cardiac volumes in the treatment field. Patients typically present with sharp, anterior chest pain and pericardial fluid causing shortness of breath and a low-grade fever. Anti-inflammatory medication and treatment interruption alleviate symptoms. With modern cardiology evaluation techniques including magnetic resonance and nuclear medicine studies, we can now identify previously unforeseen cardiac events. This is important as studies are suggesting an association between radiation therapy and the development of cardiovascular disease when the heart is an unintended target of treatment. Tangential irradiation to the left breast as treatment for breast cancer can deliver a measureable mean dose to the heart even with intensity modulation techniques [52].

Anterior-posterior treatment techniques used to treat Hodgkin lymphoma with historical non-image-guided techniques resulted in full-dose radiation therapy to multiple critical cardiac structures. In reviewing the anterior-posterior cardiac anatomy using traditional radiation therapy

treatment fields for Hodgkin lymphoma, multiple critical structures reside in the parallax of the vertebral body including the primary cardiac vessels, the electrical conduction nodes, and the aortic valve. The mitral valve resides generally 2 cm lateral to the left edge of the vertebral body in patients without chronic lung disease. Therefore, traditional radiation treatment for Hodgkin lymphoma included many cardiac structures treated at high dose, placing these tissues at risk for the lifetime of the patient. Modern cardiac imaging using multiple platforms reveals segments of the myocardium, which can demonstrate dyskinesis in small segments of the cardiac myocardium (apex) after tangential radiation therapy for breast cancer. The clinical importance of these findings is uncertain. Intensity modulation decreases radiation dose to the heart; however, there is a population treated with radiation therapy in the pre-intensity modulation era that will be at risk for the next several decades for heart disease. Recent studies demonstrate a significant risk of heart disease in the cancer survivor compared to their siblings [31, 39, 48, 52–65].

Large peripheral vessels were historically viewed as resistant to radiation therapy; however, as we begin to move forward with hypofractionation protocols, reports of injury are being reported. During historical times when treatment was delivered with orthovoltage therapy, carotid injury was described recognizing that dose to carotid was likely much higher than the reported tumor dose. Pathologies of injury include intimal hyperplasia and weakening of the carotid muscle. There are reports of fistula formation and sudden death due to rupture of the carotid vessels [31, 62]. Reports of injury to other large vessels (subclavian, femoral, etc.) were reported when there was overlap with radiation therapy treatment fields necessitating large radiation dose to a tubular structure [62]. With modern radiation therapy and traditional fractionation strategies, radiation injury to large vessels is uncommon. However, with higher daily doses to tubular structures, late injury can result and become clinically important. Symptomatic injury to veins is less common, and injury to capillaries can be visible at radiation doses of 50 Gy. This is an area, however, where retreatment of second cancers may predispose to injury in future patients.

The mechanism associated with the impact of radiation therapy on the heart and blood vessels is driven by inflammation related to the trauma of injury coupled with late fibrosis and functional instability. Intimal damage to cardiac vessels followed by cell proliferation in a disorganized manner can lead to premature coronary artery disease and atherosclerosis. Damage to cardiac valves can lead to late fibrosis and calcification which are able to cause both stenosis and insufficiency. Myocardial and pericardial inflammation can lead to muscle dysfunction, cardiomyopathy, and congestive heart failure. Pericarditis can be seen in situations where a large volume of heart receives radiation therapy and acute inflammation can lead to constriction of function. Electrical conduction deficits are seen and thought to be related to fibrosis in conduction pathways. Multiple chemotherapy agents influence cardiac health, and their relationship to injury imposed by radiation therapy remains under evaluation.

To date there is no mitigation management and therapeutic intervention available to manage cardiovascular disease driven by radiation therapy. Surgical teams need to be seasoned and expert in managing these patients. Often these experts need to both review and understand the nature of treatment and how it was applied to optimize outcome for each patient. The most optimal treatment is prevention by a seasoned radiation oncologic team with advanced knowledge of cardiac anatomy and how it can be applied to therapy with conformal avoidance and image guidance with breath-hold techniques to decrease cardiac dose. With modern radiation therapy, therapy targets are designed in four dimensions, and conformal avoidance can be applied as best as possible. Cancers are not convenient, and often cardiac structures receive both high- and low-dose radiation and cannot be avoided. In this cohort of patients, it is best to involve onco-cardiology early in the survivorship process to best ascertain imaging and functional analysis to optimize post-therapy care and identify issues in their early development when intervention may be best utilized and optimized [66].

Central and Peripheral Nervous System

The brain has several categories of cells susceptible to injury including the glia (support cells), primary neurons, and blood vessels. All of these tissues are generally considered as late-responding tissues; therefore, most sequelae occur as late events. The most important sequela is necrosis, which can occur within 6 months of radiation therapy; however, reports of late injury indicate that events can occur several years after treatment. Necrosis is seen more often now that radiosurgery techniques are used more commonly in patient care. Rarely, demyelinating syndromes can occur in the central nervous system. These syndromes can also occur in the spinal cord. Reversible syndromes can occur in the spinal cord in doses as low as 35 Gy; however, irreversible changes including myelitis begin to occur at doses of 45–50 Gy with traditional fractionation and appear to incrementally increase with larger radiation dose and larger volume of the spinal cord included in the treatment field. Toxicity may be increased with the addition of neurotoxic chemotherapy including *cis*-platinum, vinblastine, Ara-C, gemcitabine, and methotrexate. Peripheral nerves can likely tolerate a higher dose of radiation therapy as the cauda equina, and larger nerves appear to tolerate radiation doses in excess of 55 Gy without evidence of injury [67]. Visual field changes are seen in radiation doses higher than 5400 cGy to the optic nerve

and chiasm [68]. It is thought that the chiasm is sensitive to radiation therapy as it has an end-arterial blood supply. This was first described in patients treated to the pituitary gland for pituitary adenomas using daily treatment fractions of greater than 200 cGy/day [69]. Therefore, with modern-day image guidance and partial volume therapy, some investigators believe that tolerance of these structures may be higher than described in the historical literature. The cochlea can be affected by radiation, and this effect can be more pronounced at lower doses with the use of chemotherapy including *cis*-platinum. Historically the lens is very sensitive to radiation therapy with cataract formation identified at very low dose (500 cGy) [9, 70].

Brachial plexopathy has been described in breast cancer patients treated to peripheral lymph nodes. Although the radiation dose threshold for injury is thought to be 5400 cGy, this is an uncommon side effect for patients treated with higher doses of radiation for head and neck cancer. The prevailing thought is that the more sensitive part of the plexus is the region where the nerve bundles coalesce immediately inferior to the lateral third of the clavicle. In the early days of radiation therapy, this area was calculated using an anterior field to a depth of 5 cm. The nerves can be as superficial as 1 cm below the skin surface; therefore, the nerve region received a higher percent dose and in some case would have received the equivalent of a high daily fraction (>120% of the prescribed dose). This is compounded further by the use of posterior axillary boosts, which were often viewed and calculated as separate fields with exit overlap at the egress points of the brachial plexus into the upper extremity. Therefore, it is entirely possible that the threshold dose for brachial plexus injury may be higher than described in historical literature due to unintentional overlap of radiation field volumes and unspecified increases in daily fraction size to a critical target. Today, using three-dimensional volumetrics, the axilla is a volume and modern planning permits more uniform radiation dose distribution through a volume than two-dimensional treatment planning constructs [71].

The mechanism of damage to the central nervous system and peripheral nerves is multifactorial in origin. All forms of irradiation including application of orthovoltage and electrons are associated with injury. Acute changes from therapy generally affect cells with rapid self-renewal potential, relatively few cell systems in the central nervous system divide frequently, and therefore injury is generated through multiple pathways. Although damage is generated to DNA through traditional mechanisms, oxidative species generates injury to lipid bilayers, cell adhesion molecules, blood vessels, and mitochondria. The coupled imprint of primary and subcellular damage alters cell architecture and structure, thus impacting the cellular microenvironment. Vascular permeability is increased which promotes penetration of drugs into the central nervous system. Repair can be generated by stem cells residing in multiple sites of the central nervous system. If the cellular architecture and infrastructure are damaged, repair including remyelination becomes fragmented and disorganized. Irregular and disorganized regeneration of lipid bilayers is seen as leukoencephalopathy. Often injury and tumor recurrence have identical features on MR sequences and can be indistinguishable. Demyelination is frequently seen in peripheral nerves as the primary manifestation of injury as neural stem cells are sparse in peripheral locations.

Injury is often superimposed on previous changes in the central nervous system including vascular and degenerative changes, and it is often difficult to accurately assess the role of therapy on both imaging and neurocognitive testing. Medication interventions are under evaluation at this time to decrease neurocognitive changes associated with therapy. As with most organ systems, the most optimal strategy to prevent injury is to apply radiation therapy to titrated volumes when appropriate and to choose fractionation schemes to optimize repair [72, 73].

Reproductive Organs, Genitalia, and Endocrine

Spermatogonia are among the few cell systems that can die an intermitotic death; therefore, the absolute number of sperm cells markedly decreases with modest doses of radiation. The development period of stem cell to spermatozoa is 75 days; therefore, exposure to radiation can induce damage to mature sperm. In regions of nuclear events such as Chernobyl, there are reports of increased neurocognitive and developmental abnormalities in children born to survivors of these events [6]. Most oncologists offer sperm banking to patients with a known direct exposure to radiation therapy. Indirect exposure with scatter radiation dose will often require the use of birth control for two cycles of sperm development (6 months) to lessen risk of damaged sperm in the ejaculate. Leydig cells secrete testosterone, and their specific function is regulated by pituitary gonadotropins, prolactin, and luteinizing hormone. Treatment to the pituitary gland may impose secondary events to gonadal function. Although Leydig cells are more resistant to radiation exposure, there is an incremental decrease of testosterone in doses exceeding 20 Gy. Various chemotherapy agents including vincristine and mechlorethamine (Mustargen) influence sterility. Oocytes are very sensitive to radiation and, as sperm, die an intermitotic death. Because hormonal secretion is associated with follicular maturation, unlike the testicle, treatment of the ovaries results in more immediate suppression of hormonal function. Female genitalia can demonstrate mucosal atrophy and loss of moisture [15, 34, 74]. Radiation therapy to children for pelvic malignancies including rhabdomyosarcoma can result in significant atrophy and maldevelopment of gonadal organs and pelvic anatomy. Cardiovascular health

as well as other medical comorbidities including problems associated with growth can be significantly influenced by diminution of hormonal function at a young age.

Hypothyroidism is a common sequela associated with both surgery and radiation therapy to the low neck. This is quite prevalent in patients treated for head/neck cancer and Hodgkin lymphoma. Neck dissection and primary surgery also influence the incidence of hypothyroidism in patients treated for head and neck cancer. Pituitary therapy creates panhypopituitary syndrome with a need for replacement therapies as appropriate. This can have significant health issues in multiple endocrine organs. Interestingly, there is little data for adrenal function; however, there are reported cases of adrenal malfunction and decreased cortisol with high-dose radiation therapy. More often, adrenal malfunction occurs in patients as a secondary bystander effect to pituitary therapy [15, 34, 75].

Pediatrics

Treatment of children is unique as every cell system has self-renewal potential; therefore, unlike adults, sequelae are visible and identified in all tissues due to growth and development. The bone and cartilage are key areas that distinguish adults from children. In general terms, with radiation doses of 20 Gy, growth deficits in the bone may be irreversible as stem cells depopulate [34, 76]. The deficits in bone and cartilage development are more visible with higher radiation doses and younger age. In adults, the threshold dose for bone necrosis may be 55 Gy with traditional fractionation strategies; however, there are interesting reports of the use of advanced technology imaging including MR demonstrating sacral fractures in gynecological patients receiving less than 50 Gy to the bone [76]. Radiosurgery techniques, particularly to targets in close approximation to the chest wall, are reinviting injury to the rib and chest wall that is often non-healing. Treatment techniques including volume-modulated arc therapy [77] appear to play an essential role in decreasing this risk.

Recent studies have demonstrated that long-term survivors of cancer therapy, including radiation, are frailer than their counterparts and acquire chronic diseases at a higher rate. They may also be susceptible to premature death than their sibling counterparts [48].

Conclusion

Intentional and unintentional radiation exposures have a powerful impact on normal tissue function and can induce both short-term and long-term injuries to all cell systems. In the evaluation of acute phase management, assessing radiation dose and exposure is essential to management strategy. Appropriate support can be given to those at risk for serious acute injury. The effects of radiation treatment and exposure, however, last for the lifetime of the patient and can have implications for all organ systems. A broad understanding of these effects is essential for today's acute health-care provider in the emergency department setting.

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Mucositis

50

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Introduction

Mucositis is a known potential toxicity associated with several systemic chemotherapies [1], targeted therapies [2], immunotherapies [3], radiation treatments [4], and hematopoietic stem cell transplants (HSCT) [5]. Mucositis is subdivided into two main categories: oral mucositis and gastrointestinal mucositis.

Oral mucositis refers to inflammation and ulcerative injury within the oral cavity. Oral mucositis is one of the most common toxicities among patients receiving chemotherapy or targeted therapy for a variety of cancers. Oral mucositis is also commonly caused by radiation therapy or chemoradiation therapy for cancers involving the head and neck. Additionally, oral mucositis is a known adverse effect of myeloablative therapies preceding HSCT. The most common symptoms of oral mucositis are burning discomfort and pain, which often result in a difficulty eating, drinking, swallowing, and talking. These symptoms lead to decreased oral intake and, in some cases, the inability to meet nutritional and hydration needs. Patients with oral mucositis often have difficulty maintaining good oral hygiene, thereby increasing the risk of severe infection from an odontogenic source.

Gastrointestinal mucositis can occur anywhere along the gastrointestinal tract distal to the oral cavity. Injury to the gastrointestinal mucosa results in ulcerative changes similar to those seen in cases of oral mucositis. However, differences in anatomy, microbial environment, and physiology underlying the development of gastrointestinal mucositis are key reasons for this subclassification. Gastrointestinal mucositis may result in any of the following symptoms, depending on anatomic location: nausea, vomiting, abdominal cramping, diarrhea, rectal pain, or rectal bleeding. Decreased oral intake is a common downstream effect of gastrointestinal mucositis.

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Mucositis is a dose-limiting toxicity and may result in premature discontinuation of anti-neoplastic therapies. Further, severe cases of mucositis may require hospitalization. Treatment interruptions due to premature discontinuation of therapy or hospitalization are linked to poor oncologic outcomes such as increased risk of disease recurrence and decreased overall survival.

Case Study

A 65-year-old male with a 35-pack-year smoking history presented to his dentist with a nonhealing oral ulcer. Physical exam revealed a large ulcerative lesion over the left tongue with associated induration of the surrounding tissue. A biopsy of the lesion demonstrated P16-negative squamous cell carcinoma. A CT of the head and neck revealed asymmetric thickening of the left tongue as well as an enlarged left level 2 lymph node. An FDG-PET CT demonstrated FDG avidity associated with the left tongue as well as the left level 2 lymph node, but no evidence of distant metastasis. The patient underwent a hemiglossectomy and bilateral neck dissection demonstrating SCC measuring 3.0 cm in the left tongue with a depth of invasion of 10 mm and multiple positive lymph nodes in the left neck. Margins were focally positive. The patient was recommended to undergo postoperative chemoradiation treatment to the oral cavity and bilateral neck to a maximum dose of 66 Gy in 33 fractions with concurrent weekly cisplatin. During the third week of chemoradiation, the patient complained of discomfort in his oral cavity when eating. Physical exam revealed grade 1 oral mucositis. Over the following 2 weeks, the patient experienced progressive pain in his oral cavity, decreased oral intake, and weight loss exceeding 10% of his total body weight. Physical exam during the fifth week of chemoradiation revealed grade 3 oral mucositis. During the patient's sixth week of treatment, the patient was hospitalized for sepsis and failure to thrive, requiring discontinuation of chemoradiation.

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History/Background

Over the past several decades, there have been a few improvements to anti-mucositis agents [6]. While some agents have been shown to decrease the severity and duration of mucositis, there are no known curative agents. Despite the number of randomized studies suggesting a benefit to anti-mucositis agents, the results often lack reproducibility, making development of treatment guidelines a challenge. Thus, mucositis remains a significant problem both for cancer patients and their physicians.

Anatomy

The oral and gastrointestinal mucosae arise from the endoderm and consist of a continuous membrane lining the entirety of the alimentary tract from the oral cavity through the anal canal. There are several layers that comprise the mucosa including most superficially (interiorly) the epithelium, followed by a layer of connective tissue, followed by a muscular layer (muscularis mucosa). The mucosae overlie a layer of dense connective tissue known as the submucosa. The purpose of the mucous membrane is to secrete mucous, providing a barrier to pathogens.

Pathophysiology

The pathogenesis of injury to the oral and gastrointestinal mucosa is characterized by five key phases: initiation, upregulation, signal amplification, ulceration, and healing [7]. Anti-neoplastic therapies, such as chemotherapy and radiation, are known to cause both direct and indirect injuries to the oral and gastrointestinal mucosa. Direct tissue injury occurs when double-stranded DNA breaks induce apoptotic signaling and the production of reactive oxidative species. In turn, pro-inflammatory cytokines are released, such as TNF-α and IL-1β, and NF-κB signaling pathways are activated, which play a key role in the pathogenesis of mucositis [8, 9] (Fig. 50.1). Indirect tissue injury occurs when anti-neoplastic therapies reduce the mucosal barrier through villus blunting and crypt ablation. The combination of direct and indirect tissue injury leads to signal amplification and exacerbated tissue injury.

Several studies have demonstrated the impact of the local tissue microbiome on the pathogenesis of mucositis. Differences in the microbiome in the oral cavity compared to that of the gastrointestinal tract help to explain some of the site-specific reactions to therapeutic agents. Bacterial ligands of resident gastrointestinal flora not only regulate the mucosal immune response to anti-neoplastic agents but also play an important role in mucosal regeneration [10].

The physiologic mechanisms underlying the symptoms caused by mucositis also vary depending on anatomic location. In the small bowel, mucosal injury to enteric cells results in the release of 5-hydroxytryptamine (5-HT), serotonin, and substance P. These chemicals act as neurotransmitters and stimulate the dorsal brainstem, leading to symptoms such as nausea and vomiting [6, 11]. In the colon, mucosal injury results in the release of pro-inflammatory cytokines, which stimulate a neuronal feedback signal resulting in diarrhea.

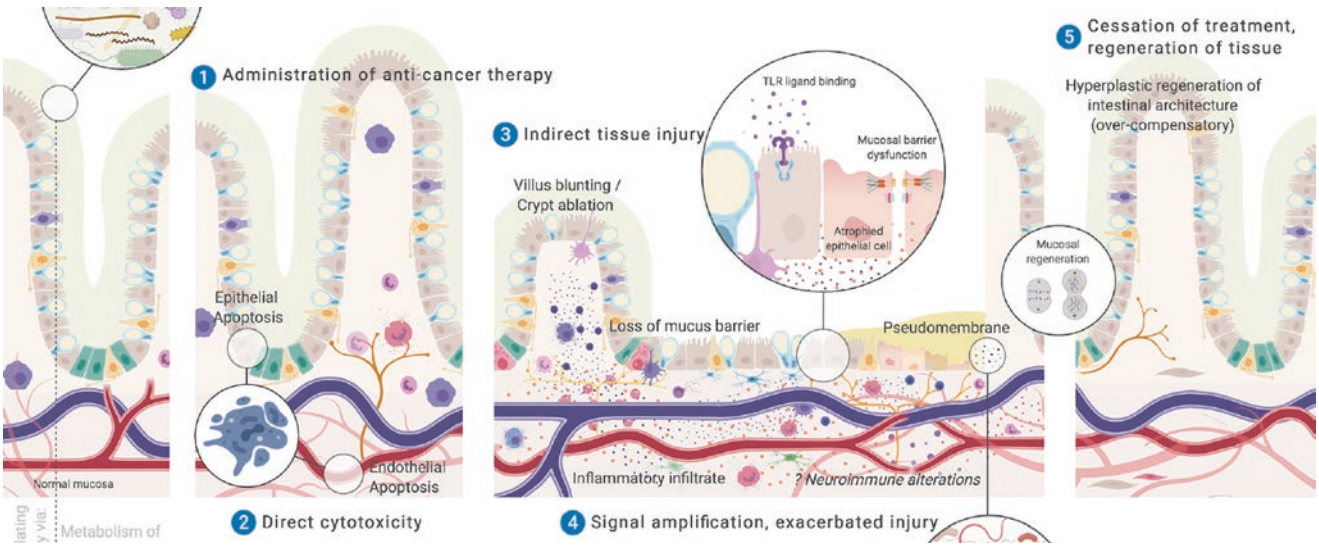

Fig. 50.1 The pathogenesis of mucosal injury. Anti-neoplastic therapies (1) cause both direct (2) and indirect (3) mucosal injuries, which result in activation of TNF-α and IL-1β, and NF-κB signaling pathways (4). The local tissue microbiome exerts immunomodulatory effects and plays a role both in mucosal damage and regeneration (5). (Adapted from Bowen et al. with permission [8] Springer Nature)

Epidemiology

Approximately one fifth of advanced cancer patients will experience mucositis [12]. Of those, 60% will experience a decrease in oral intake, 40% will experience severe impairment of nutrition or hydration, and 6% will experience complete prevention of nutrition or hydration due to mucositis. Of the approximate 440,000 patients receiving chemotherapy annually in the USA, more than one third will experience mucositis [13]. Of the 20,000 hematopoietic stem cell transplants in the USA annually, at least 87% of patients will experience mucositis [14].

Patients with cancer arising from the head or neck are at particularly high risk of developing oral mucositis, with an odds ratio of 6.31 [6]. In 2020, there will be an estimated 65,630 new cases of head and neck cancer diagnosed in the USA [15] and 650,000 new cases worldwide [16], and at least 80% undergoing radiation for head and neck cancer will experience mucositis [17].

Individuals at the greatest risk for the development of mucositis include the pediatric and geriatric populations. 80% of pediatric patients receiving chemotherapy experience oral mucositis [18] and 99% of pediatric patients undergoing hematopoietic stem cell transplant [19] experience either oral or gastrointestinal mucositis. Geriatric patients comprise a majority of new cancer cases and tend to have poor tolerance of oncologic therapies. Further, geriatric patients often recover more slowly from anti-neoplastic toxicities than do younger patients.

Health Economics

Cases of oral and gastrointestinal mucositis have a significant economic impact. A study published in 2008 reported that the total median medical costs of patients with mucositis or pharyngitis related to anti-neoplastic therapy were $39,313 [20]. These costs were approximately double that of the total median medical costs of $20,798 for patients without therapy-induced mucositis. The largest contributor to increased medical costs for patients with mucositis is extended inpatient hospitalizations, which can occur as a result of the potential sequelae of mucositis, such as infection or nutritional deficiency. A report based on data from 2012 estimated a combined cost of $15,500 for every inpatient hospitalization due to severe mucositis [21].

Toxic mucositis results in annual costs of $13.23 billion in the USA [6]. Cases of grades 1–2 mucositis account for roughly 60% of the total cost burden, and cases of grades 3–4 mucositis account for the remaining 40%.

Indirect costs of mucositis relate to the amount of time spent by physicians and clinical staff managing patient's symptoms of mucositis. Nurses and physicians spend an additional 9.0 and 5.7 hours, respectively, per head/neck cancer patient managing mucositis during their treatment course [22].

Presentation

The symptoms associated with mucositis vary depending on the anatomic location of the mucosal injury. Patients with oral mucositis initially present with a burning sensation in the oral cavity or oropharynx, which progresses to pain. Pain associated with oral mucositis can range from mild to severe and may result in difficulty chewing or swallowing, unintentional weight loss, or the inability to maintain oral hygiene. Oral mucositis increases the risk of infection and, in some cases, can result in hospitalization or premature discontinuation of anti-neoplastic therapy. Based on patient-reported data, the approximate duration of oral mucositis in patients undergoing radiation treatment is 70–84 days and 68–102 days in those undergoing chemotherapy (4–6 cycles) [17, 23].

Patients with gastrointestinal mucositis present with inflammatory symptoms and, depending on the anatomic location of mucosal injury, can be characterized as pharyngitis, esophagitis, gastritis, colitis, or proctitis. Patients with mucositis-related pharyngitis or esophagitis may experience odynophagia, dysphagia, or retrosternal pain. Patients with mucositis-related gastritis or colitis may experience nausea, vomiting, abdominal cramping, or diarrhea. Patients experiencing mucositis-related proctitis may experience pain with bowel movements or rectal bleeding.

Diagnosis

Oral mucositis can be diagnosed by inspection of the oral cavity for erythema, edema, and ulceration of the oral mucosa. Detection of mucosal injury distal to the oral cavity is more challenging. Endoscopy allows for the visualization of mucosal changes; however, endoscopy is not recommended in patients with suspected or presumed mucositis, as it may lead to further tissue injury. There are ongoing studies of non-invasive methods to aid in the diagnosis of mucositis, though these methods have not been adopted as common practice. For example, esophageal mucositis is associated with mucosal thickening identified on CT-based imaging [24]. Similarly, bowel wall thickening visualized on ultrasound may indicate inflammation related to gastrointestinal mucositis [25]. Additional studies are aimed at identifying one or more biomarkers associated with mucositis. At this time, gastrointestinal mucositis largely remains a clinical diagnosis made based on the presence of patient-reported symptoms.

Table 50.1 Comparison of mucositis assessment tools

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
RTOG/EORTC [27]	Irritation or erythema of the mucosa; may experience mild pain; may require topical analgesic; may require soft diet; <5% weight loss from pretreatment baseline; nausea, abdominal discomfort, and increased frequency of bowel habits not requiring intervention	Patchy mucositis that may produce an inflammatory serosanguinous discharge; may experience moderate pain; may require narcotic analgesics; may require puree or liquid diet; <15% weight loss from pretreatment baseline; may experience nausea, vomiting, abdominal pain, or diarrhea requiring intervention	Confluent fibrinous mucositis; may include severe pain requiring narcotic; >15% weight loss from pretreatment baseline requiring feeding tube, IV fluids or hyperalimentation; nausea, vomiting, abdominal pain/distention despite medication	Ulceration, hemorrhage, or necrosis; perforation or fistula; ileus; obstruction; GI bleeding requiring transfusion; abdominal pain requiring tube decompression or bowel diversion	N/A
WHO [26]	Mild symptoms; oral soreness, erythema	Moderate symptoms; oral erythema or ulcers, solid diet tolerated	Severe symptoms; oral ulcers with extensive erythema, requiring liquid diet only	Life-threatening symptoms; requirement for parenteral or enteral support	N/A
NCI CTCAE [28]	Erythema of the mucosa; minimal discomfort; normal diet; not interfering with function; intervention not indicated	Patchy ulcerations or pseudomembranes; symptomatic but can eat and swallow; modified diet; no interference with activities of daily living; medical intervention indicated	Confluent ulcerations or pseudomembranes; bleeding with minor trauma; symptomatic and unable to adequately aliment or hydrate orally; stool incontinence or other symptoms interfering with activities of daily living	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death

RTOG Radiation Therapy Oncologic Group, *EORTC* European Organisation for Research and Treatment of Cancer, *WHO* World Health Organization, *NCI CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events

There are several criteria by which the severity of mucositis can be classified. Grading systems include the World Health Organization (WHO) scale for mucositis [26], the Radiation Therapy Oncologic Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC) toxicity criteria [27], and the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) [28] (see Table 50.1). Examples of oral mucositis grades 1–4 based on the WHO grading scale can be seen in Fig. 50.2. Other assessment tools include the Oral Mucositis Assessment Scale (OMAS) [29] and the patient-reported outcome measure (PROM) scale [30].

Prophylaxis and Management of Oral Mucositis

Anti-inflammatory Agents

Benzydamine is an anti-inflammatory agent used for the prevention and treatment of oral mucositis. Benzydamine inhibits prostaglandin synthetase, thereby blocking the production of pro-inflammatory cytokines such as TNF-α and IL-1β. Benzydamine is currently the only agent for which there is level 1 evidence supporting its use in the management of mucositis. Benzydamine mouthwash can be used both for the prophylaxis and treatment of oral mucositis in patients receiving chemotherapy alone, radiation treatment alone, or concurrent chemoradiation to the head/neck [31, 32]. Randomized studies have demonstrated that benzydamine improves pain [33] as well as severity of oral mucositis [34]. However, benzydamine may not control radiation-induced oral mucositis at radiation doses greater than 50 Gy [35–37].

Irsogladine maleate is an anti-inflammatory agent that inhibits the production of reactive oxidative species. There are data demonstrating a benefit of systemic irsogladine maleate for the prevention of chemotherapy-induced oral mucositis [38].

Rebamipide is an anti-inflammatory agent with several mechanisms of action that ultimately promote mucosal protection. One randomized study demonstrated a decrease in the severity of oral mucositis in patients receiving chemoradiation treatment in patients using rebamipide mouthwash compared to placebo [39].

Oral Cryotherapy

Oral cryotherapy is the method of cooling the oral cavity either by ice or cold liquids. Oral cryotherapy results in local vasoconstriction, reducing the exposure of mucous membranes in the oral cavity to cytotoxic agents present in systemic therapies. Evidence supports its use in the prevention of chemotherapy-induced mucositis, especially in patients receiving fluorouracil-based chemotherapy or high-dose melphalan-based therapy preceding HSCT [40, 41].

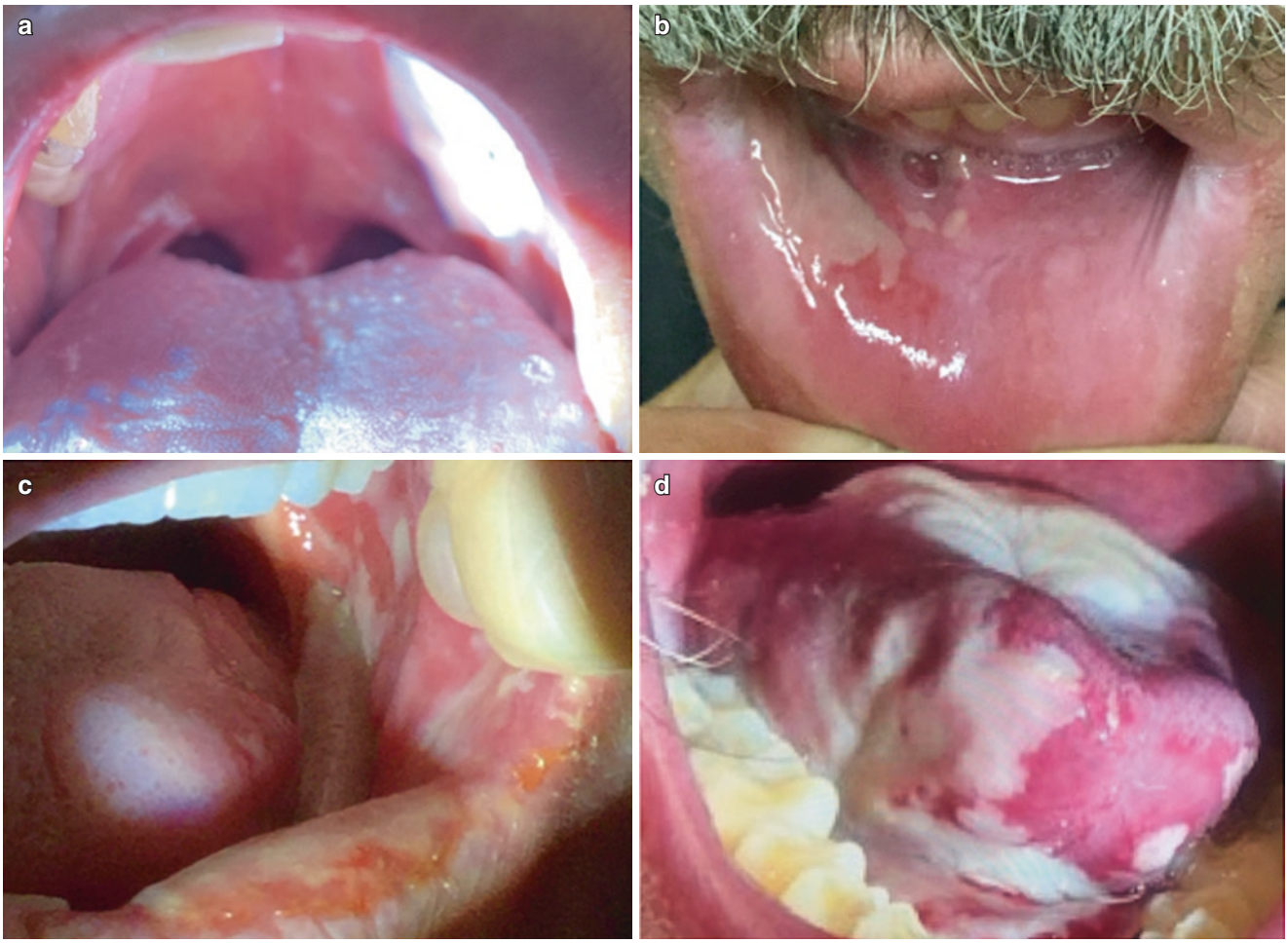

Fig. 50.2 Examples of oral mucositis on physical exam according to the WHO [26]. Panel (**a**) is an example of WHO grade 1 mucositis, characterized by erythema of mucous membranes. Panel (**b**) is an example of WHO grade 2 mucositis, characterized by the presence of oral ulcers. Panel (**c**) is an example of WHO grade 3 mucositis, characterized by the presence of extensive ulcers causing a need for liquid diet. Panel (**d**) is an example of WHO grade 4 mucositis, characterized by the presence of severe mouth sores inhibiting oral intake

Ease of administration and cost-effectiveness are additional benefits of oral cryotherapy. In comparing anti-mucositis agents, oral cryotherapy is suggested to be the best intervention to reduce the incidence of oral mucositis with a few side effects [42].

Palifermin

Palifermin is a keratinocyte growth factor that induces the epithelial cell proliferation in the oral and gastrointestinal mucosa. Palifermin results in cytoprotective effects, decreases the production of pro-inflammatory cytokines, and promotes mucosal regeneration. Palifermin is recommended for the prevention of oral mucositis in patients undergoing high-dose chemotherapy and total body irradiation prior to HSCT. Data have suggested that palifermin reduces both the severity and duration of oral mucositis in patients undergoing HSCT [43]. The recommended dose of palifermin for the prevention of oral mucositis is 60 ug/day for 3 days prior to conditioning treatment and 3 days following stem cell transplant [5, 44]. A common side effect of palifermin is taste disturbance [42].

Photobiomodulation

Photobiomodulation (PBM), also referred to as low-level light therapy or low-level laser therapy, consists of nonionizing light sources. PBM has been shown to promote wound healing and decrease inflammation following mucosal injury. Several randomized studies have demonstrated the benefit of intraoral PBM for the prevention of oral mucositis in patients undergoing HSCT [45]. Studies have also demonstrated a benefit of intraoral PBM for the prevention of radiation-induced oral mucositis. PBM used for the prevention of oral

mucositis should be delivered at a wavelength of 650 nm, power of 40 mW, and tissue energy dose of 2 J/cm^2 [5, 44].

Opioid Analgesics

Patient-controlled morphine has been recommended for the management of severe oral mucositis in patients undergoing HSCT [5]. There is no evidence to demonstrate the superiority of continuous infusion morphine over patient-controlled morphine; however, patient-controlled morphine is associated with less total consumption [46]. Topical morphine, in the form of mouthwash, has been shown to reduce the severity of oral mucositis in patients undergoing radiation, chemotherapy, or chemoradiation therapy for cancer of the head/neck [47, 48]. Transdermal fentanyl has been shown to be both safe and effective in managing pain due to chemoradiotherapy-related oral mucositis [49].

Gabapentin

Gabapentin is a structural analog of gamma-aminobutyric acid (GABA), an amino acid that acts as an inhibitory neurotransmitter. Gabapentin is known for its effectiveness as an antiepileptic, though it is also commonly used in the treatment of neuropathic pain. There are data supporting the use of gabapentin for reduction of pain associated with radiotherapy-induced oral mucositis [50, 51]. Gabapentin can reduce or completely eliminate the need for opioid pain medications. The recommended dose of gabapentin for oral mucositis is 2700 mg daily.

Doxepin

Doxepin hydrochloride is a tricyclic antidepressant shown to have analgesic and anesthetic effects when used topically. Studies have demonstrated a statistically significant reduction in pain related to oral mucositis among patients undergoing radiotherapy for head and neck cancer using doxepin oral rinse [52, 53].

Nutritional Supplements

Glutamine is an amino acid that promotes cellular proliferation and survival. Oral glutamine has been shown to delay the onset, and reduce the severity of, oral mucositis in patients receiving chemoradiotherapy to the head and neck [54, 55]. The recommended dosage is 10−30 mg per day, and it is available in various formulations including a mouth rinse as well as oral forms.

Zinc is an electrolyte that promotes homeostasis, wound healing, and immune responses. Several randomized studies have demonstrated the benefit of zinc in the prevention of oral mucositis among patients receiving radiation or chemoradiation treatment to the head/neck [56, 57].

Elemental diet formulations are nutrient-rich liquids and may be beneficial in preventing oral mucositis in patients undergoing radiation treatment to the head/neck [58].

Vitamin E is an antioxidant with anti-inflammatory properties. Studies have shown a benefit of vitamin E for the treatment of chemotherapy-induced oral mucositis [59, 60]. Topical vitamin E, available in a mouth rinse, appears to be more effective than in pill form [61]. There are data suggesting a benefit to vitamin E in preventing radiation-induced oral mucositis as well [62].

Natural Agents

Honey has been shown to reduce the severity of radiation-induced oral mucositis [63]. Honey functions both as an antimicrobial and also to maintain the integrity of the mucosal epithelium. The high sugar content of honey increases the risk of dental caries; therefore good dental hygiene practices are crucial for patients using honey.

Aloe vera has both anti-inflammatory and antimicrobial properties, and it has been shown to modulate the immune system when delivered orally [64]. There are data to suggest that aloe vera reduces both the incidence and the severity of oral mucositis in patients undergoing radiation to the head/neck [65, 66]. Additional studies are needed to identify the optimal dose of aloe vera, as high concentrations can result in diarrhea and drug interactions [67].

Curcumin is a compound found in turmeric with anti-inflammatory, antioxidant, and antitumor properties [68]. Turmeric mouthwash has been shown to delay the onset of mucositis and decrease the severity of mucositis in patients undergoing radiation therapy for cancer of the head/neck [69, 70].

Oral Care

Professional oral care and routine oral hygiene practices performed at home by patients may reduce the severity of oral mucositis and the risk of infection from odontogenic sources. Studies have shown that professional dental evaluation and treatment reduces the severity of oral mucositis and improves pain associated with oral mucositis [71]. Patient education is recommended to improve patient compliance with oral hygiene practices at home. Patients should also be instructed to drink plenty of water and avoid painful stimuli such as hot or spicy foods or liquids, smoking, alcohol, and objects that

may cause trauma to the oral cavity (e.g., ill-fitting dentures). There have been studies demonstrating a benefit to saline or sodium bicarbonate mouth rinses in reducing the severity of oral mucositis. A multi-agent regimen is recommended to optimize oral care in patients undergoing chemotherapy, HSCT, or radiation to the head/neck.

Prophylaxis and Management of Gastrointestinal Mucositis

Amifostine

Amifostine is a prodrug with several mechanisms of action related to the scavenging of free radicals and DNA repair. A recommended dose of 340 mg/m^2 of intravenous amifostine can be administered for prevention of radiation-induced proctitis [29]. There are also data suggesting a benefit for amifostine to reduce esophageal mucositis in patients undergoing radiation treatment for non-small cell lung cancer [72].

Octreotide

Octreotide is a somatostatin analog that causes arterial vasoconstriction. Octreotide is best known for its use in the management of acute gastrointestinal bleeding. There are data to suggest the use of intramuscular octreotide in the treatment of diarrhea associated with HSCT, but only following a failed trial of loperamide [44].

Sucralfate

Sucralfate is an agent best known for its use in peptic ulcer disease. Sucralfate functions both as an acid buffer and a protective barrier for gastrointestinal mucosa. Prior studies have suggested its benefit for radiation-induced proctitis [73, 74].

Antimicrobials

The use of oral antibiotics ciprofloxacin and metronidazole was studied in a randomized trial for the treatment of chronic radiation-related proctitis and demonstrated a benefit [75, 76].

Antihistamines

Histamine receptor antagonists, such as famotidine, may be useful for the prevention of gastrointestinal mucositis in patients undergoing radiation treatment for prostate cancer, though additional studies are needed [77].

Nutritional Supplements and Dietary Modifications

Numerous modified diets have been studied for efficacy in the prevention and management of gastrointestinal mucositis. There is no clear benefit of fat-modified diets, fiber supplementation, or prebiotic supplementation. However, there are data to support the use of oral glutamine to reduce the severity of radiation-induced esophagitis [78–80] and to decrease the duration of diarrhea in patients undergoing HSCT [81]. Probiotics, or oral formulations of live bacterial species found in normal gut flora, may be useful in the prevention of chemotherapy or radiation-induced diarrhea [82, 83].

Formalin

Topical formalin reduces superficial mucosal blood flow [84], and data suggest a benefit in cases of hemorrhagic radiation-related proctitis [85].

Palifermin

In addition to using palifermin for the prevention of oral mucositis, it has been shown to decrease the severity of chemotherapy-induced and HSCT-related gastrointestinal toxicity [86, 87].

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBO) is a treatment modality by which 100% oxygen is delivered in a pressurized chamber. HBO results in the production of reactive oxygen and nitrogen species, which promote tissue healing via several molecular pathways. HBO has been studied in the context of late radiation toxicity, and data support the use of HBO for treatment of late radiation-related proctitis [88].

Disposition/Follow-Up

Patients with a history of therapy-induced mucositis should receive regular oncologic follow-up, at which time they can be evaluated for long-term effects of mucosal injury. Patients recovering from mucositis may benefit from follow-up with a dietician. There are several screening tools to

evaluate patients for chronic nutritional deficiency, such as the malnutrition universal screening tool (MUST) and the NUTRISCORE tool [89, 90].

Prognosis/Treatment Complications

Most cases of acute therapy-related mucositis will resolve with time. Significant risks associated with mucositis include severe infections, dehydration, and weight loss. Such infections and severe malnutrition result in unexpected treatment breaks or premature discontinuation of anti-neoplastic therapies and are associated with increased rates of recurrence and worse survival. Patients should be monitored closely with additional nutritional support including a feeding tube if needed and routine IV hydration.

Common Pitfalls

Patients at high risk of oral and gastrointestinal mucositis should be identified prior to initiating therapy. Education regarding the symptoms of mucositis and the importance of oral hygiene and nutrition should precede initiation of therapy. Patients at risk for developing mucositis should undergo thorough evaluation by both a dental health professional and a dietician. Throughout the course of therapy, patients should be screened weekly for weight loss and for symptoms of mucositis. Early intervention with intravenous fluid hydration and/or enteral feeding tube placement is critical in patients experiencing rapid, continuous weight loss and can reduce the risk of hospitalization or treatment break.

Future Needs/Vision

Despite the growth of literature pertaining to anti-mucositis agents, guidelines continue to lack specific recommendations for many agents studied in the prevention and management of oral and gastrointestinal mucositis. The range of anatomic sites of mucositis development, as well as the numerous therapies known to cause mucositis, results in highly specific studies. Furthermore, the distinction between prevention of mucositis and treatment of mucositis is important due to differences in the mechanisms of early compared to chronic mucosal injury. Ongoing studies should further elucidate the pathogenesis of mucositis, and their results may be valuable in identifying potential targets for anti-mucositis agents.

Residency and fellowship training should include formal didactics pertaining to the diagnosis, documentation, and management of oral and gastrointestinal mucositis.

Health Services/Resource Use

Educational resources for patients and physicians can be found via the Multinational Association of Supportive Care in Cancer (MASCC) [5], an organization that has published its recommendations for the management of mucositis. The European Society for Medical Oncologic (ESMO) and the National Comprehensive Cancer Network (NCCN) have published their own sets of clinical guidelines [44, 91].

Documentation

Mucositis is often underreported by physicians. Patient-reported duration and severity of mucositis are typically longer and worse compared to that reported by physicians [92]. The cause of underreporting is multifactorial. However, the attitude among health professionals that toxicities related to therapy are "normal" and fear among physicians that adverse events will reflect poorly on their practice may be contributing factors [93, 94].

Key Points/Pearls

- Pathogenesis of mucositis is mediated by pro-inflammatory cytokines released as a result of both direct and indirect mucosal injuries. Ongoing studies are aimed at elucidating the role of the microbiome in the pathogenesis of mucositis, as well as the process of mucosal regeneration/healing.
- Diagnosis of oral mucositis is based upon physical exam; however, the diagnosis of gastrointestinal mucositis is based on patient symptoms aided by the use of patient-reported assessment tools.
- Early nutritional intervention and counseling are recommended for patients at risk of developing mucositis. Nutritional counseling by a dietician specializing in oncologic, dental evaluation by a dental health professional, and education regarding the importance of routine oral hygiene practices are recommended for those patients identified as high risk.
- Evaluation of patients early in the course of therapy for symptoms of mucositis is critical to reduce the likelihood of hospitalization or treatment interruptions, which are associated with worse oncologic outcomes.

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Stoma Complications

51

Patricia A. Brock and Kumar Alagappan

Introduction

Creation of a stoma in the course of cancer treatment is common and may lead to complications seen in the emergency department (ED). The United Ostomy Association estimates that slightly more than 500,000 Americans now have some type of stoma. Annually in the USA, roughly 100,000 people undergo the creation of either a colostomy or ileostomy. The incidence is increasing due to the rising prevalence of colorectal cancer and diverticular disease in this country [1]. More than 75% of stomas are placed as part of the management of colorectal cancer [2]. This surgically created opening placed in the abdomen is felt to be a simple procedure; however, consequences can be complex, serious, and costly to the healthcare system. Data regarding complication rates is lacking but is thought to range from 21 to 70% in one review [3], while another study reports morbidity ranging between 31 and 60% [1]. Stomas are formed in both the gastrointestinal and urogenital tracts as a means of redirecting stool and urine content, respectively. They can be permanent or temporary. Some are placed after a planned surgical procedure, while others follow an emergency operation. Surgical advancements improving ostomy care include enhanced recovery after surgery as well as new robotic and laparoscopic techniques. Additionally, ostomy equipment enhancements provide better appliance options for patients [4].

Case Study

A 49-year-old female underwent a subtotal colectomy and proctectomy with end ileostomy formation. She had initial difficulties with leakage, but follow-up with the stomal therapist led to a proper pouching system and she remained leak-free. Three weeks postoperatively, she presented to the ED with high stomal output (4–5 L/day) and an elevated creatinine. Her abdomen was nontender. She received IV fluids in the ED and was admitted to the hospital. Stool studies were negative, and her diarrhea was controlled through dietary manipulation and addition of antidiarrheal medication.

Classification

Intestinal ostomies are classified according to the segment of the bowel brought to the surface. Ileostomies or small-bowel ostomies are often located on the left side of the abdomen. In the USA, an estimated 165,000–265,00 individuals live with this type of ostomy at the rate of 40,000 new ostomies annually [5]. This is distinguished from colostomies, which originate from the large bowel and are most often on the left side of the abdomen. Ostomies can either be a terminal or end ostomy with the bowel divided and the proximal stump brought to the surface. Alternatively, a loop ostomy is created when the anterior wall of the bowel is brought to the surface and is not transected.

A urostomy is made in cases where drainage of urine through the bladder and urethra is not possible, as in the case of a cystectomy following the diagnosis of invasive bladder cancer, the sixth most common cause of cancer in the USA.

Factors such as body habitus and pre-existing conditions contribute to poor outcomes. Although most issues arise in the first 5 years postoperatively, the risk of complications from stoma formation can last throughout one's life and can affect daily activities for the patient [4]. Early complications include inappropriate placement, skin irritation, soilage, stoma retraction, dehydration, and stoma necrosis. Late complications include stomal prolapse, peristomal hernia, chronic dermatitis, and orifice narrowing. Compounding ostomy complications in cancer patients are issues related to ongoing treatments with chemotherapy, immunotherapy, and radiation, as well as the increased prevalence of malnutrition and weight loss.

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When evaluating the ostomy/stoma, physicians should be familiar with common complications and be ready to call for a surgical consult, if needed, especially if unfamiliar with the device.

Health Economics

A 2017 study by Taneja et al. estimated the cost of peristomal skin complications in the USA. In their retrospective cohort of 128 patients undergoing colostomy, ileostomy or urostomy (cancer and non-cancer related), they found that one-third experienced peristomal skin complications within 90 days and that total healthcare costs were almost $80,000 higher for these patients in comparison with those without such complications [6]. In addition to economic costs, cancer survivors with ostomies face a number of challenges related to self-care. Bulkley et al. surveyed 177 long-term rectal cancer survivors with ostomies, finding that the majority reported ongoing challenges, most commonly leakage around the pouching system and peristomal skin problems [7]. In a more recent study, Sun et al. found that the greatest challenges posed by ostomies were associated with the use of ostomy appliances and time requirements for ostomy care [8]. Additionally, they noted bleeding, pain, leakage, skin problems, and ostomy cleaning as challenges. Patients reported anxiety related to leakage, odor, and skin irritation as barriers to social activity and self-confidence. To prevent ostomy-related ED visits, enhancements in community-based, ostomy self-management initiatives may hold promise. In 2018, Hornbrook et al. estimated the cost of an ostomy nurse-led, small-group program, and concluded that a five-session training course conducted over 8 weeks would cost $1812 per patient [9]. Given the high cost of stoma complications, this expense would appear to provide a cost benefit.

Diarrhea

Daily volumes exceeding one liter above baseline generally define the presence of ileostomy-associated diarrhea. When portions of the ileum and the colon are not available for normal fluid absorption, excess liquid and the accompanying electrolytes are eliminated through the ileostomy. Adaptive changes occur after the initial postoperative period in many patients, but in some, this condition, also referred to as high-output stoma, is troublesome and can be dangerous [5]. High-output stomas occur in 16% of stomas created [10]. In the early postoperative period, 16–50% of patients report high-output diarrhea, and nearly 20% require readmission as a consequence [5].

When presenting to the ED, this complaint is often associated with dehydration and electrolyte imbalances. Close attention to renal function is necessary as having an ileostomy is a risk factor for kidney failure [5]. Large sodium losses with high volumes of fecal waste may occur, leading to hyponatremia. Poor absorption of magnesium also occurs. Evaluation for an obstruction or an infectious etiology, most commonly, *Clostridium difficile*, is important. Risk factors for high stomal output include the use of diuretics, coexisting diabetes mellitus, and having undergone a total proctectomy [10].

Diarrhea associated with a colostomy is described as having loose or watery bowel movements more than four times in 1 day. Although benign causes such as a change in diet may be the culprit, more severe etiologies include infection or an intestinal blockage.

After a thorough medical history, noting prior surgeries and oncologic interventions, the emergency evaluation of a patient presenting with diarrhea will include laboratory analysis of the electrolytes and renal function, as well as close attention to the volume status of the patient, which may be manifested by a low blood pressure or an elevated heart rate. Skin turgor and mucus membranes should be noted, and palpation and auscultation of the abdomen may detect tenderness or signs of obstruction. The clinician should directly examine the stoma and its contents. Stool analysis for an infectious process, most commonly, *C. difficile*, is important. A review of all medications for prokinetic properties, including metoclopramide, laxatives, erythromycin, etc., is imperative. Metformin may provoke increased stomal output, as can an abrupt discontinuation of steroids. Review of dietary changes may be informative. Imaging should be ordered only if an obstructive etiology is considered or pain is a prominent feature of the presentation.

Initial management should focus on fluid management, electrolyte replacement, and control of the diarrhea. If tolerated, fluid resuscitation may be provided via the oral route, with isotonic drinks the best option. Avoid intake of hypotonic drinks, tea, coffee, alcohol, and fruit juices. In most cases, however, adequate venous access will be important. IV supplementation of electrolytes will be guided by laboratory results. Cardiac monitoring may be necessary in the setting of severe electrolyte derangements. Most commonly used antimotility agents include diphenoxylate/atropine and loperamide. In several randomized studies of established ostomies, loperamide reduced output by 22–30% [5]. The typical dose is 4 mg four times per day before meals and at bedtime.

In severe cases where outputs are over 3–4 L per day, octreotide can be used [5]. However, if considering octreotide, the patient will likely require a general surgery consultation and admission.

If available, consultation with an experienced enterostomal therapist could provide assurance of a good device fit and reinforce the patient's knowledge of daily maintenance.

Decisions for inpatient admission or observation are made based on labs, volume status, and whether the patient tolerates fluids orally.

Skin Irritation

Despite the improvement of ostomy systems and study of the creation and care of the stoma, skin complications remain a common occurrence following colostomy, ileostomy, or urostomy surgery. Its occurrence is reported to be 43%, most commonly after an ileostomy [11]. Skin irritation is related to the caustic, watery content of the frequent movements, which contain proteolytic enzymes and a high pH [12]. Ill-fitting appliances leading to areas of the skin exposed to erosive content may be a consequence of normal ostomy maturation, and the remedy may be as easy as proper adjustment of wafer size [13]. However, prevention of this complication should begin in the operating room with creation of a quality stoma protruding 2–3 cm above the skin surface [4]. Additionally, poor placement of the ostomy in relation to body folds makes secure application of the appliance difficult. Regular assessment of the pouching system may avert the skin irritations that can become cyclic if left unchecked. Infectious causes, mainly fungal, also result in skin irritation and are seen in immunocompromised and diabetic patients (Fig. 51.1) [14].

Visual inspection of the intact ostomy bag is key, noting whether the selected wafer size matches the ostomy. Examination of the skin may reveal an erythematous papular rash consistent with candidiasis. This rash may be present under the wafer as well as in the skin surrounding the stoma. An allergic contact dermatitis, often due to an ostomy care product, may produce papules, vesicles, and redness. The patient will complain of itching and burning.

Ensuring proper wafer placement is often aided by a referral to an ostomy specialist. To manage suspected contact dermatitis, change the product currently being used, add a skin sealant to the local area, and make an outpatient referral to a stomal specialist or a dermatologist. Irritant dermatitis responds well to topical corticosteroid lotions [13]. Nystatin powder is the optimal treatment when candidiasis is suspected.

Hernia

A parastomal hernia (PSH) can occur with either an ileostomy or colostomy [15] and is variably reported to have a

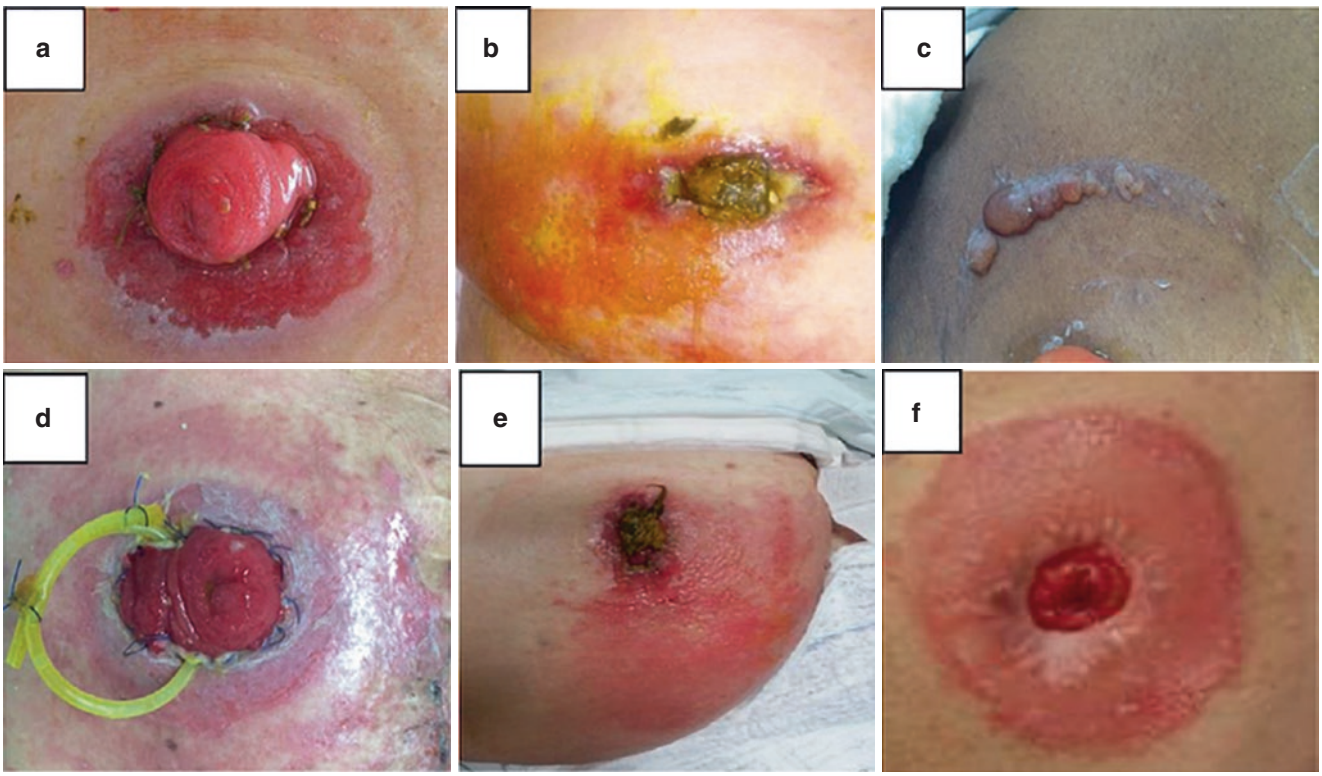

Fig. 51.1 Peristomal dermatitis. Irritation caused by the effluent in an inadequate pouch adaptation to the skin allowing the prolonged feces/skin contact (**a**) and an early pouch detachment (**b**). Blister at the adhesive area in the periphery of pouch resin itself (**c**). Dermatitis caused by both pouch resin and peripheral adhesive (**d**). Dermatitis due to contact of feces with the skin (**e**). Fungal dermatitis (**f**). (From Rodrigues et al. [14] with permission CC by 3.0)

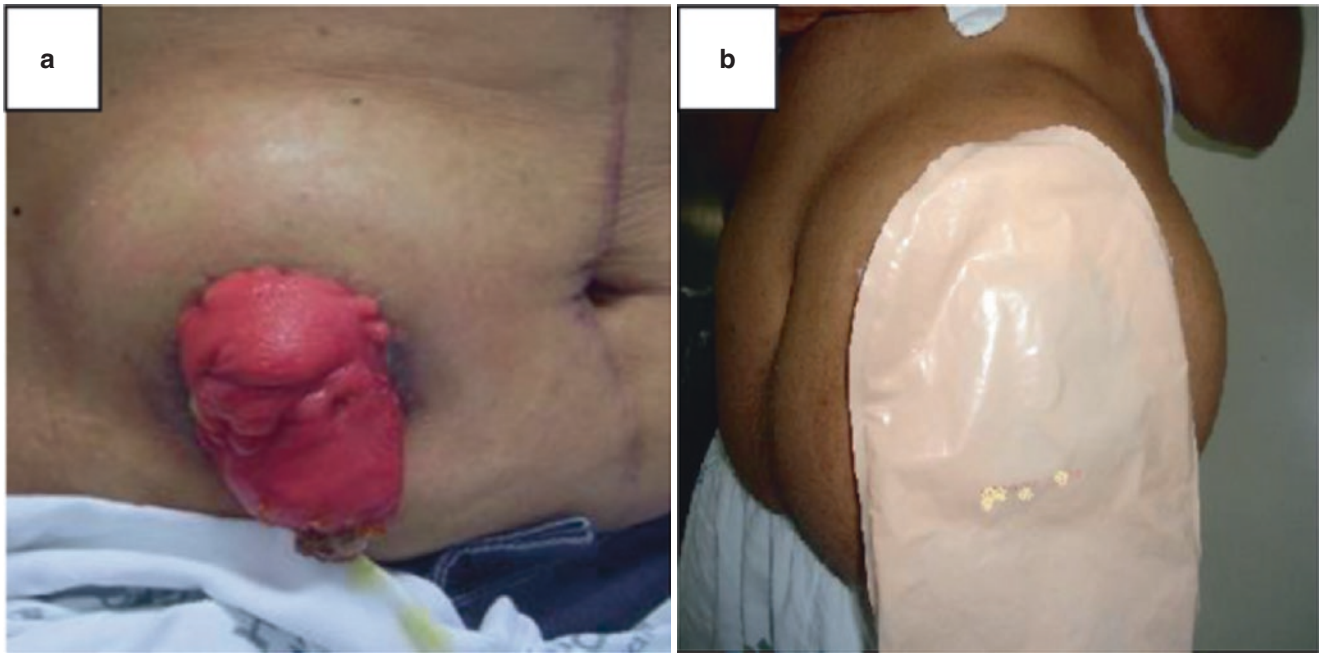

Fig. 51.2 Parastomal hernia in a prolapsed stoma (**a**) and a huge parastomal hernia (**b**). (From Rodrigues et al. [14] with permission CC by 3.0)

3–50% incidence due to a wide range of definitions [10]. Most are asymptomatic, but as they grow these hernias can cause problems. End colostomy has a higher rate of parastomal hernias. A late complication of ostomy surgery, PSH is symptomatic in 75% of patients but can lead to a reduced quality of life. Symptoms range from esthetic complaints, discomfort, local pain, leakage, and poor appliance application to emergent presentations with strangulation and obstruction. Risk factors for the development of a hernia are either patient-related or attributed to a technical problem. Perioperative steroid use has also been cited as a factor [16] (Fig. 51.2).

Clinical examination is necessary for the diagnosis of parastomal hernia. Direct inspection can be challenging, as detection of a bulge and cough impulse is a subjective finding. Details of the fascial defect and concomitant incisional hernias, as well as other occult pathologies, may obscure the diagnosis. In addition, clinical detection of PSH can be challenging in the obese patient. When diagnostic uncertainty exists, computed tomography and ultrasonography may be useful adjuncts. Nonurgent surgical evaluation is advised, unless a surgical emergency is suspected.

The majority of peristomal hernias are managed conservatively with the aid of a stoma care nurse advising the patient on proper appliance placement and improved adhesive adjuncts, as well as supportive garments. Outpatient referral for elective surgical intervention should be considered for those with high symptom burden. However, the patient presenting with a picture of bowel obstruction and/or signs of intestinal ischemia requires expeditious surgical consultation and resuscitation while preparing for a possible eminent operative procedure.

Retraction

Although usually seen acutely in the immediate postoperative period due to ischemic changes, retraction can be a late stoma complication. Retraction is the inversion of the mucocutaneous junction toward the abdominal wall. Poor fitting of the stoma appliance results in spillage of stool contents and skin irritation/inflammation. The latter is likely the reason for ED presentation (Fig. 51.3). In mildly symptomatic patients, a change in the stomal appliance may be useful to decrease bowel leakage. In severely symptomatic patients, a surgical referral for revision is necessary.

Stenosis

A stenosis or stricture of an ostomy can cause a mechanical obstruction to the passage of bowel contents. The patient presents with symptoms ranging from constipation to crampy abdominal pain. Ischemia of the bowel at the level of stoma may be causative; in patients with a prior history of Crohn's or malignancy, this may represent a recurrence. A narrowing of a colostomy may result from local infection or inadequate skin opening. Strictures associated with ileostomies most often require definitive surgical treatment. Those associated

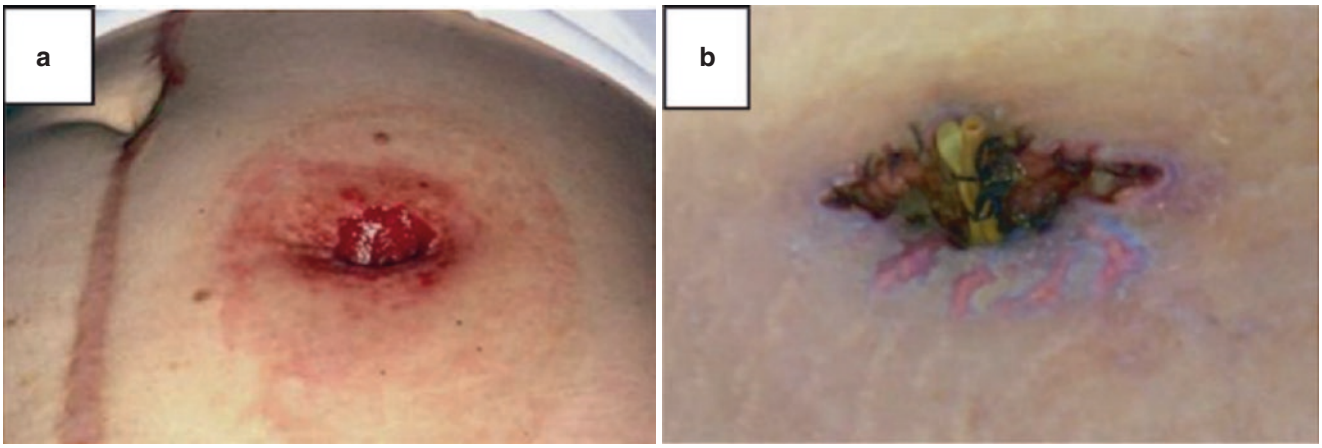

Fig. 51.3 Ostomy retraction with light (**a**) and severe (**b**) inflammatory reaction. (From Rodrigues et al. [14] with permission CC by 3.0)

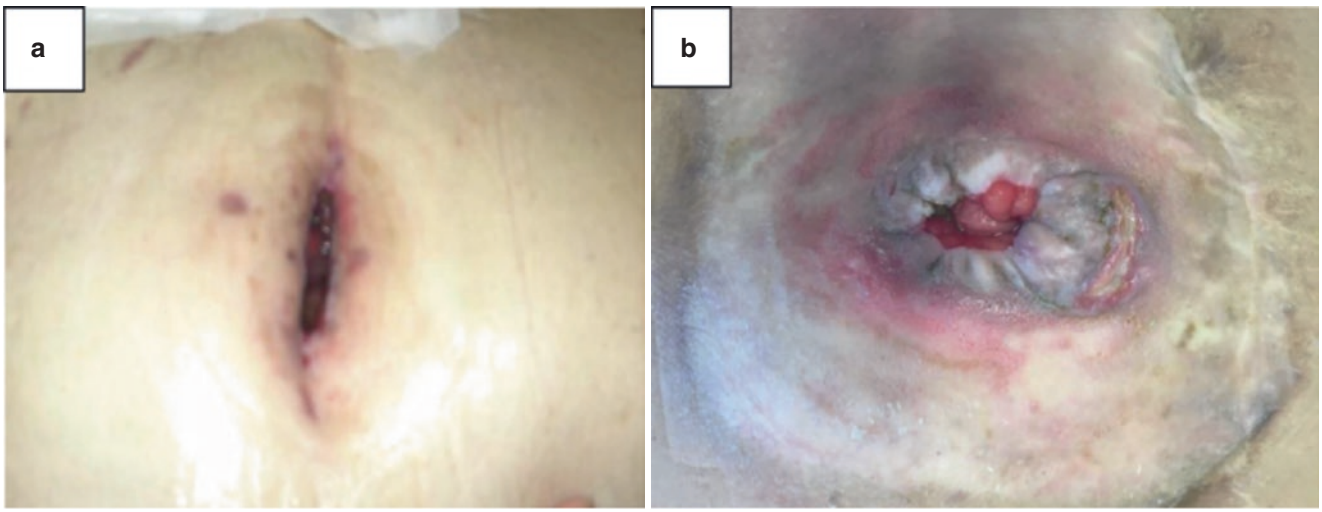

Fig. 51.4 Stoma stenosis. Note the retraction of the skin (**a**) and the scar tissue around the stoma opening in a chronic stoma stenosis (**b**). (From Rodrigues et al. [14] with permission CC by 3.0)

with colostomies may respond to dietary modifications and expectant management (Fig. 51.4).

In addition to a thorough abdominal assessment, examination of the stoma is critical. Digital inspection to the level of the fascia will yield important information regarding the degree of stenosis. Imaging will be required if obstruction is suspected.

Minor stenosis can be managed by changes in diet. However, symptomatic patients with obstructive symptoms require a surgical consultation and management. Management may include dilatation of the stoma with a 36 Fr Foley as a temporizing maneuver.

Prolapse

Stomal prolapse occurs as a late complication with the patient presenting to the ED with a segment of bowel protruding through the stomal opening. Occurring more often in the transverse loop colostomies [10], a prolapse can occur with any stoma and has a reported incidence between 2–26% [16]. This complication is found more often in obese patients and may be due to the original surgical technique. Although this is an unsightly and distressing complication, it is usually of little clinical significance. However, left untreated it can result in incarceration and strangulation from edematous bowel (Fig. 51.5).

Symptoms include skin irritation, difficulty with appliance application, and bleeding from the mucosa secondary to exposure. There is a low risk of bowel obstruction, incarceration, and strangulation associated with stomal prolapse.

The patient's history of an acute onset versus intermittent prolapse will supplement the necessary digital inspection of the ostomy for bowel viability. Further workup for bowel strangulation or obstruction should be conducted as indicated.

Some prolapses are amenable to bedside reduction. With significant bowel edema, however, osmotic therapy with

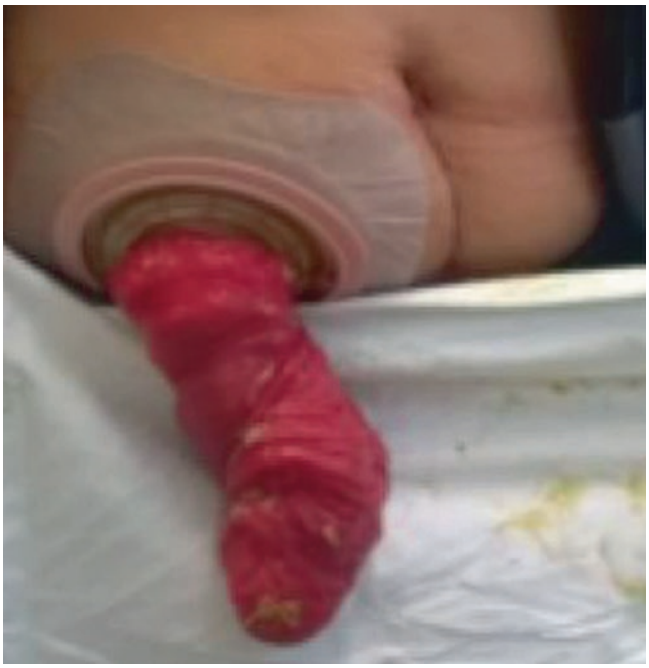

Fig. 51.5 Stoma prolapse. Note the abnormal length of the stoma. If left untreated the ostomate is more susceptible to abrasions or infection. (From Rodrigues et al. [14] with permission CC by 3.0)

simple table sugar applied to the prolapsed stoma and allowed to sit for 30 minutes may allow for a reduction [10]. Outpatient referral can be considered for further evaluation along with adjustment in pouch size. If viability of the bowel is in question, a surgical evaluation is necessary in the ED.

Bleeding

Local stomal bleeding is a rare occurrence. Local trauma can cause visible blood related to improper pouching technique or a rigid appliance encroaching on the mucosa. Recurrent trauma can lead to exuberant granulation tissue that is friable and bleeds frequently. A more consequential reason for profuse bleeding may be stomal or parastomal varices. Although usually appearing in the presence of portal hypertension, blockage of vessels within the mesentery can result in mucosal venous congestion and bleeding. In patients with a diagnosis of cirrhosis, this is a recognized ectopic site for variceal development. In some cases, these varices can be singular causes for focal bleeding. Variceal bleeding is usually painless, profound, and recurrent [17].

While digital examination of the stoma is of prime importance for local bleeding, consideration of a source anywhere along the gastrointestinal tract should be entertained and dealt with in a similar manner as in any patient with a GI bleed. Most bleeding from a stoma will have a visible site of injury or a bleeding vessel. If this is not evident, treat the patient as if they were having a GI bleed. The majority of cases of peristomal varices can be easily identified on physical exam by a bluish hue in the peristomal skin and presence of caput medusae in the peristomal area [16].

Local manual pressure is the first therapeutic maneuver with acute stomal bleeding. A useful adjunct is an epinephrine-soaked gauze. Isolated minor trauma-related bleeding will stop with local pressure and time. Granulation tissue associated with chronic local trauma is treated with local destruction by silver nitrate or judicious electrocautery. Suturing of a visible vessel can be considered, but ligation of a bleeding varix is often futile and long-term success unlikely. Mortality is high due to underlying severe liver disease. Medical and/or surgical consultation should be obtained which will focus on reduction of portal pressure.

Urostomy Complications

Urinary diversion following cystectomy for bladder cancer management is increasing in prevalence [18]. When a urostomy is created, it is either incontinent or continent, and the patient will be familiar with the type constructed. The incontinent urostomy drains into a stoma bag attached via an appliance. The continent urostomy requires intermittent catheterization in order to drain the urine.

The ileal conduit, an incontinent urostomy, is the most common type of urinary diversion following cystectomy, accounting for 85% [19]. Typically created from the terminal ileum, these stomas have a lower risk of electrolyte imbalance.

The continent urostomy uses either the ileum or colon, or a combination of both, as a reservoir. Patients are instructed to routinely self-catheterize to avoid complications such as urinary tract infections, hydronephrosis leading to upper pole injury, stone formation, and perforation.

Metabolic derangements commonly occur in patients with intestinal urinary diversions due to the absorptive surface of the bowel.

Future Needs

The creation of a stoma represents a major life event that will affect a rising number of individuals, especially as the rate of colorectal cancer accelerates. The healthcare system will be impacted, and the ostomate will continue to face the potential of complications throughout their life.

Several innovative strategies to mitigate these effects might include:

1. *Prehabilitation* is a preoperative tactic to identify and address the malnutrition and physical deconditioning present in cancer patients as well as identify psychological needs of those requiring an ostomy [20]. Adding a

robust and comprehensive discharge plan with patient education material [21] combined with referral to a support group and a connection to a stomal expert would be part of this process.

2. *Centralizing information* regarding optimal practice patterns, including knowledge about basic ostomy care, ostomy product availability, and standardized care plans, has been advocated to improve clinical outcomes [22].
3. Proactive monitoring of *patient-reported outcome measures* (PROMs) has been utilized, leading to improved adaptation to life after ostomy surgery. PROMs may play a role in physical and psychological adaptation [23].
4. Adding *ostomy telehealth* services for cancer survivors could expand the options for meaningful follow-up for ostomates, especially new ones, whose use of resources outstrips other colorectal patients [24, 25].

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Hematopoietic Cell Transplant

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Introduction

Hematopoietic cell transplantation (HCT) has the potential to cure both malignant and nonmalignant hematologic diseases that may not be possible with conventional therapy. HCT allows for the administration of high-dose chemotherapy and radiotherapy while providing an opportunity for hematologic recovery with stem cell reinfusion. In the context of allogeneic HCT, an immunologic attack against the tumor cells is also conferred, termed graft-versus-tumor (GVT) effect.

Broadly, HCT consists of three phases: conditioning, stem cell infusion; and, for allogeneic HCT, graft-versus-host disease (GVHD) prophylaxis. The choice of conditioning regimen, stem cell source, and GVHD prophylaxis depends on patient and disease characteristics, as well as donor availability. The purpose of conditioning regimen is to eliminate tumor cells resistant to conventional doses of chemotherapy and, in the case of allogeneic HCT, produce sufficient immunosuppression to prevent graft rejection. Conditioning regimens used prior to autologous HCT are myeloablative, characterized by irreversible marrow aplasia requiring stem cell rescue. For allogeneic HCT, conditioning regimens can be classified as myeloablative; nonmyeloablative, which cause minimal cytopenias and can be given without stem cell support; and reduced-intensity, which result in intermediate degrees and duration of marrow suppression [1]. The source of stem cells can be from bone marrow, peripheral blood, or umbilical cord blood. HCT can also be categorized according to the relationship between the donor and recipient [autologous, syngeneic, or allogeneic (matched related, matched unrelated, or haploidentical)].

In 2018, approximately 23,000 HCTs were performed in the Unites States; of these, over 60% were autologous and the remainder were allogeneic. The most common indication for autologous HCT is multiple myeloma followed by lymphoma (non-Hodgkin and Hodgkin). Acute leukemias (acute myeloid leukemia, acute lymphocytic leukemia) and myelodysplastic syndrome (MDS) are the most common indications for allogeneic transplants, accounting for 75% of allogeneic HCTs [2]. Nonmalignant conditions that can be treated with HCT include, but not limited to, aplastic anemia, thalassemia, and autoimmune disorders (e.g., systemic sclerosis).

Complications of High-Dose G-CSF Administration

The most commonly used agent for hematopoietic cell mobilization and collection is granulocyte colony-stimulating factor (G-CSF), which triggers neutrophil elastase and cathepsin G to cleave bone marrow adhesion molecules, such as vascular cell adhesion molecule-1, stromal cell-derived factor, and CXCR4 [3, 4]. It is administered generally for 4 days before apheresis, with the goal of mobilization and increasing the total white blood cell (WBC) in the peripheral blood, of which a fraction is CD34+ stem cells. The majority of adverse events (AEs) associated with G-CSF are minor and not life-threatening, including bone pain, particularly along the back, pelvis, and/or ribs (82–94%); headache (34–70%); body aches; fatigue; and nausea/vomiting; however, serious and life-threatening AEs have been reported, including splenic rupture and ischemic complications, which constitute oncologic emergencies [4].

Splenic Rupture

The Research on Adverse Drug Events and Reports (RADAR) project reviewed AEs associated with G-CSF administration [5]. In addition to the common toxicities mentioned above, they also reported rare instances of

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splenic rupture, allergic reactions, flares of underlying autoimmune disorders, lung injury, and vascular events [5]. Several studies have evaluated short-term administration of G-CSF on spleen size, with an average increase of 10% in volume and 11 mm in length occurring in 95% of subjects [6]. Although spleen size returned to baseline ~10 days after completion of G-CSF, instances of splenic rupture have been reported in the literature. While rare, a small number of case reports note a timing of rupture between day 3 and day 10 after the first G-CSF administration with outcomes ranging from those requiring conservative measures or splenectomy and even death [5]. An open-label study evaluating splenic changes in normal donors found that a predicted twofold change in spleen volume occurred in donors 60 years of age or older, although the physiological changes accounting for this phenomenon are unknown [6]. The leading hypothesis comes from pathologic evaluation of ruptured spleens requiring splenectomy, with histology indicating extramedullary myelopoiesis possibly leading to expansion of the hematopoietic tissue in the spleen.

Ischemic Complications

Ischemic complications have also been reported after G-CSF administration, especially in individuals with known coronary artery disease (CAD). In a study by the American College of Cardiology aiming to mobilize progenitor cells from the bone marrow to promote myocardial neovascularization and relief of ischemia, no objective evidence of cardiac benefit was found; rather, there were concerns for potential adverse outcomes. Their study of 16 patients reported 2 patients with serious AEs:

1. A 52-year-old diabetic man with a history of 2 myocardial infarctions (MIs) and class III angina, despite prior percutaneous coronary intervention (PCI), who developed severe chest pain, nausea, and diaphoresis with electrocardiogram (ECG) showing new ST-segment depression and mild ST-segment elevation treated with enoxaparin and nitroglycerin paste.
2. A 69-year-old man with class IV angina, history of MIs and 16 PCIs, coronary artery bypass, transmyocardial laser revascularization, and enhanced external counterpulsation, who experienced 3 episodes of angina without ECG changes, was ultimately hospitalized 2 weeks later for severe chest pain, and developed electrical-mechanical dissociation followed by asystole and death [7]

These individuals are extreme examples of baseline cardiovascular disease and would unlikely meet criteria for an ASCT; however, even rigorous testing with echocardiograms and ejection fraction cutoffs with input from cardiology consultation may not always identify patients at high risk for cardiovascular complications during the transplant process. Hence, it is standard practice at the Fred Hutchinson Cancer Research Center (FHCRC) to admit patients for G-CSF mobilization on telemetry if they have known CAD and a history of cardiac disease and, particularly, AL amyloidosis patients who may or may not have cardiac involvement. The pathophysiology behind exacerbations of underlying CAD by G-CSF is unclear, but in vitro experiments have shown that pro-inflammatory markers such as C-reactive protein (CRP) may play a role in promoting plaque destabilization and rupture.

Complications of Apheresis

Once the level of CD34+ cells is adequate in the peripheral blood, the process of apheresis is initiated for collection and storage of these progenitor cells. In general, apheresis is relatively safe but can also lead to serious, albeit manageable, complications. One of the most commonly encountered complications is citrate-induced hypocalcemia, as it is used as an anticoagulant throughout the apheresis procedure. Citrate will complex calcium, resulting in hypocalcemia in upward of 9% of treatments and leading to symptoms of perioral or distal extremity paresthesias [8]. If not reversed, severe citrate-induced hypocalcemia may prolong the QTc and lead to cardiac arrhythmias, in addition to muscle spasm, chest pain, and hypotension. Infusion providers are aware of this common complication and readily supply calcium tablets or intravenous calcium to mitigate hypocalcemia. Other commonly encountered phenomena after apheresis are thrombocytopenia and anemia, which may be further pronounced in a patient who recently received cytotoxic therapy or with bone marrow infiltration from their underlying disease. Various mechanisms for thrombocytopenia may contribute, and decreases of platelet count up to 50% have been reported, especially with older apheresis devices. Coupled with anemia and a hematocrit drop of up to 10%, hemorrhage may occur after an apheresis procedure [8]. Providers should be aware of these transient decreases in blood counts, monitor levels accordingly, and have a low threshold to work up any evidence for vital sign changes and signs or symptoms reminiscent of hemorrhage. Patients should be counseled on the potential need for transfusions even without bleeding events.

DMSO Toxicity

Dimethyl sulfoxide (DMSO) is the most commonly used cryopreservation agent for autologous stem cells collected via apheresis, protecting cells from the injurious effects of

freezing and crystal formation prior to storage. While relatively nontoxic to patients in small amounts, reinfusion of DMSO with the thawed autologous stem cells may trigger complications as much as 20–50% of the time in the acute setting, ranging from uncomplicated to serious toxicities [9]. Manageable or expectant side effects can be seen such as skin flushing, nausea, vomiting, diarrhea, and abdominal cramping brought about by a vagal response upon intravenous infusion of the cold product; however, sudden and severe toxicities have also been reported [9, 10]. These include cardiovascular or respiratory complications such as sudden and severe hypotension, bradycardia, fatal arrhythmias, dyspnea, respiratory arrest, and diffuse alveolar hemorrhage [9, 10]. Serious neurologic complications such as reversible leukoencephalopathy, strokes, and epileptic seizures have also been reported [11]. These serious toxicities are presumably from histamine-induced vasodilation and release; therefore, DMSO toxicity may result in increased morbidity and prolonged hospital admissions and incur additional treatment-related costs. In a survey from 444 European Bone Marrow Transplantation (EBMT) centers to assess DMSO-related complications, 95 centers completed the questionnaire for a 22% response rate. Of the 95 responding centers, 57 reported at least 1 DMSO toxicity (60%). Approximately 34,000 transplants were carried out by the 95 centers, giving an overall incidence of 1.4%, or approximately 1 in every 70 transplants [12].

Case Study

A 64-year-old male with IgG kappa multiple myeloma ultimately receives his cryopreserved autologous peripheral blood stem cells and experienced no major complications; however, he now presents with vomiting, debilitating oropharyngeal pain, and diarrhea 6 days after stem cell infusion with a conditioning regimen consisting of melphalan 200 mg/m^2. The patient was treated supportively with antiemetics, loperamide (after a negative stool Clostridium difficile test), intravenous fluids, patient-controlled analgesia, and total parenteral nutrition.

By day + 14, the patient noted improvement in symptoms with supportive management. However, on day + 16, the patient developed new-onset generalized erythematous rash, fever, and 3-kg weight gain. CBC with differential count showed a hemoglobin of 8.6 g/dL, white blood cell count of 1.5 K/uL, absolute neutrophil count (ANC) of 540/uL, and platelets of 19 K/uL. Comprehensive metabolic panel is remarkable only for hypokalemia at 3.6 mEq/L and slightly elevated creatinine at 1.3 mg/dL (baseline 0.8 mg/dL). Blood and urine cultures were negative. Chest X-ray showed slightly increased interstitial markings but no consolidation.

Oral Complications of HCT

Oropharyngeal mucositis (OM) is a common complication that typically peaks 6–11 days following high-dose conditioning regimens and then eventually heals over 1–2 weeks [13]. Recombinant keratinocyte growth factor (palifermin) is occasionally given with conditioning regimens, particularly those that include total body irradiation (TBI), to reduce the incidence of severe OM [14, 15]. Adverse reactions with palifermin include rash, oral dysesthesia, tongue thickening and discoloration, as well as taste alteration. With high-dose melphalan conditioning, oral cryotherapy (use of ice chips) is instituted to reduce the severity and duration of OM [16].

The development of OM may predispose patients to systemic bacterial infections originating from the mouth flora (e.g., *Streptococcus viridans* or *S. mutans*). In addition, when severe, OM may increase the risk for aspiration and airway compromise [13]. Bleeding may occur with OM, but is often minimal given platelet-support protocols and routine herpes simplex virus (HSV) prophylaxis [13]. Treatment is supportive with regular oral hygiene, saline rinses, mucosal coating agents (e.g., antacids), and topical anesthetics. Caution is advised when recommending topical anesthetics due to the risk of inadvertent mucosal injury while eating or performing oral care while the mouth is temporarily anesthetized. Oral anesthetics may also impair the gag reflex, increasing the risk of aspiration. When local measures are inadequate in providing relief, systemic pain management with opioid patient-controlled analgesia is usually effective.

Concurrent infection can accentuate the severity of OM. Candidiasis and HSV are common oral infections after HCT. However, the routine use of antifungal and antiviral prophylaxis has dramatically reduced the incidence and extent of these infections. When suspected, swabbing of the oral ulcers or lesions for histopathologic examination and culture should be performed.

Parotiditis is another oral complication typically seen among patients who are receiving total body irradiation and high-dose chemotherapy [17, 18]. Treatment is supportive with analgesics, warm compresses, and stimulation of salivation (i.e., lemon drops).

Gastrointestinal Complications of HCT

Following most conditioning regimens, nausea, vomiting, and diarrhea are common. Adequate control of nausea and vomiting is important not only for patient comfort but also to prevent complications such as dehydration, malnutrition, electrolyte or metabolic derangements, aspiration, erosive esophagitis, and esophageal tears.

Although chemotherapy-induced diarrhea is common after conditioning, patients should be ruled out for *C. difficile*, which is the most common cause of diarrhea in healthcare settings [19]. Because *C. difficile* colonization occurs in approximately 10–15% of HCT patients [20] and current testing is not capable of differentiating true disease from colonization, it is important to carefully select patients appropriate for testing. *C. difficile* testing is indicated in patients with new-onset diarrhea defined as three or more loose stools in 24 hours [19]. The preferred drug for treating an initial episode of *C. difficile*-associated diarrhea is vancomycin (125 mg PO QID × 10 days) because it has been shown to result in superior clinical cure compared to metronidazole [19]. However, metronidazole (500 mg PO TID × 10 days) is an acceptable alternative if oral vancomycin is not available. In patients with significant diarrhea despite active *C. difficile* treatment, loperamide may be considered as an adjunct, but should be approached with caution because there have been no prospective or randomized studies supporting its safety in the context of active *C. difficile* infection [19, 21, 22].

During the expected period of profound neutropenia following HCT, patients can develop neutropenic enterocolitis (NEC) (also termed typhlitis, ileocecal syndrome, or necrotizing enterocolitis). It is manifested as fever, nausea, vomiting, diarrhea, and abdominal pain [23]. The pathogenesis likely involves chemotherapy-induced disruption of the gastrointestinal mucosa and transmural translocation of pathogens [24]. Polymicrobial infection is frequent with gram-negative bacilli, gram-positive cocci, anaerobes (*C. septicum*), and even fungal infection, most commonly by *Candida* spp. The diagnosis is based on clinical presentation and radiologic findings. Contrast CT can demonstrate bowel thickening or dilation, mesenteric stranding, and pneumatosis [25]. Management includes supportive therapy with bowel rest, intravenous fluids or parenteral nutrition (if indicated), and antimicrobial therapy. Empiric antibiotics should cover enteric gram-negative and anaerobic pathogens. Piperacillin-tazobactam (Zosyn) or dual therapy with cefepime plus metronidazole is preferred. The carbapenems (imipenem-cilastatin and meropenem) are alternative agents for patients allergic to the recommended antibiotics or suspected to have resistant gram-negative bacteria, such as an extended-spectrum beta-lactamase (ESBL)-producing organisms [26].

Engraftment Syndrome

Neutrophil engraftment is defined as an ANC ≥500/uL for three consecutive days, whereas platelet engraftment is defined as an unsupported platelet count ≥20,000/uL. The timing for neutrophil engraftment typically occurs 2–3 weeks after stem cell reinfusion, but largely varies on patient and disease characteristics, stem cell source, and dose and conditioning regimen.

Engraftment syndrome (ES) can occur as a complication of autologous HCT, approximately 4–5 days before and after neutrophil recovery [27, 28]. ES is likely mediated by the release of pro-inflammatory cytokines. It encompasses a range of clinical manifestations such as noninfectious fever, rash, diarrhea, organ dysfunction, and features of capillary leak (noncardiogenic pulmonary edema, weight gain) with no alternative etiology other than engraftment [28]. Although no definitive biomarkers of ES have been identified, elevated levels of C-reactive protein have been associated with ES [29, 30]. The diagnosis of ES is clinical, and a standard diagnostic criterion has not been established. The Spitzer [27] and Maiolino [31] diagnostic criteria for ES have been proposed (Table 52.1).

Differences in diagnostic criteria used likely account for the wide range (7–90%) of reported incidence [32]. Because the clinical presentation of ES can be seen with infection, a comprehensive workup for infectious sources should be performed. If infection is ruled out, systemic corticosteroids can be used for treatment with favorable responses, although the majority of ES cases are mild and self-limited.

Peri-engraftment respiratory distress syndrome (PERDS) likely represents a pulmonary-predominant presentation of ES. PERDS can be defined by the presence of fever, hypoxia, and diffuse lung infiltrates on radiographs in the absence of infection, cardiac dysfunction, or fluid overload, within 5 days of neutrophil recovery [33]. Bronchoalveolar lavage

Table 52.1 Proposed diagnostic criteria of engraftment syndrome

	Spitzer criteria [27]	Maiolino criteria [31]
Requirements	3 major *or* 2 major +1 minor	Major +1 minor
Major criteria	Noninfectious fever (≥101 °F) Erythrodermatous rash over >25% of the body not linked to medication Noncardiogenic pulmonary edema	Noninfectious fever
Minor criteria	Weight gain (2.5% increase) Hepatic dysfunction (bilirubin ≥2 mg/dL or a twofold increase in transaminase over baseline) Renal dysfunction (twofold increase in serum creatinine over baseline) Transient encephalopathy	Skin rash Pulmonary infiltrates Diarrhea
Timing of symptoms relative to engraftment	96 hours within ANC 500/uL	Commencing 24 hours before or at any time after the appearance of neutrophils

ANC absolute neutrophil count

(BAL) can assist in ruling out infection and assessing for diffuse alveolar hemorrhage (DAH). DAH is characterized by the return from BAL becoming progressively bloodier or demonstrating ≥20% iron-laden macrophages on staining [34]. When no infectious etiology is identified, the primary therapy for both PERDS and DAH is with systemic corticosteroids. However, a higher dose of steroids is recommended for DAH, given as pulse doses of methylprednisolone 1 g daily, whereas in ES or PERDS, the dose of steroids is 0.5–1 mg/kg prednisone equivalent daily.

Autologous GVHD

A GVHD-like syndrome may occur in patients following autologous HCT, termed autologous GVHD. Although there may be overlapping clinical manifestations observed in ES and autologous GVHD, both are generally considered as distinct syndromes. Autologous GVHD is supported by histologic findings of classic GVHD (apoptosis with or without lymphoid infiltrate). The pathogenesis of autologous GVHD is not well understood, but is hypothesized to be related to immune dysregulation and inappropriate recognition of self-antigens [35]. Autologous GVHD is clinically and histologically similar to traditional acute GVHD, and can involve the skin, liver, and, most commonly, the GI tract [36]. Systemic corticosteroid is the mainstay of therapy and generally effective. Mild cases of autologous GVHD involving the skin can be treated with topical steroids only.

Transfusion-Associated GVHD

Transfusion-associated GVHD (TA-GVHD) is a rare but usually fatal complication of blood-component transfusion therapy. TA-GVHD occurs when viable donor lymphocytes proliferate in susceptible patients after transfusion. Patients with primary immunodeficiency syndromes, hematologic malignancies, and following HCT are at risk for TA-GVHD. The clinical features of TA-GVHD are similar to those of traditional GVHD but with an earlier onset, generally occurring 7–10 days after transfusion [35]. Patients may present with rash, fever, transaminitis, diarrhea, or abdominal pain [37]. One distinguishing clinical feature of TA-GVHD is profound pancytopenia; this increases the risk of infections, the most common cause of death in TA-GVHD, often occurring 3–4 weeks after the diagnosis [35]. Given the lack of effective therapy for TA-GVHD and its high fatality rate (80–90%), prevention of TA-GVHD is critical [38]. Irradiation of whole blood and cellular components is the only widely adopted technique to prevent TA-GVHD. Irradiation inactivates donor T lymphocytes, thereby abrogating the potential for GVHD. The US Food and Drug Administration recommends irradiation at a dose of 2500 cGy [38]. In addition to using irradiated blood products, patients with hematologic malignancy and following HCT should also only receive blood products that are leukoreduced to avoid alloimmunization and cytomegalovirus (CMV) transmission.

Acute Complications After Allogeneic HCT

Acute toxicities related to high-dose chemotherapy used as part of conditioning prior to autologous or allogeneic HCT are similar. However, allogeneic HCT is associated with distinct acute complications not present after autologous HCT due to the presence of donor cell alloreactivity (graft-versus-host disease (GVHD)), immunosuppressive medications used to prevent or treat GVHD and prevent graft rejection, and the resulting greater degree of host immunosuppression. Here we discuss acute complications unique to allogeneic HCT recipients.

Acute Infectious Complications After Allogeneic HCT

In recipients of HCT, the risk of infection is greatest during the period of pancytopenia following conditioning chemotherapy and/or radiation, but persists for 6–12 months after autologous HCT and up to 24 months following allogeneic HCT, due to the need for B- and T-cell immune reconstitution. In the allogeneic transplant recipient, this may be exacerbated by ongoing need for immunosuppression for prevention or treatment of graft-versus-host disease (GVHD). Prior to engraftment after HCT, mucosal and cutaneous damage from the conditioning regimen presents the main risk for infection. Neutropenic fever is common during this period and occurs in most patients. In the early period (<100 days after HCT), a variety of infections can occur, as summarized in Table 52.2. Specific pathogens which are important to consider in the HCT recipient are also outlined in Table 52.2.

Veno-Occlusive Disease (VOD) (Previously Termed Sinusoidal Obstruction Syndrome)

Liver complications after allogeneic HCT have become less frequent over time due to better understanding regarding the prevention and treatment of serious hepatobiliary problems. The use of ursodeoxycholic acid, a hydrophilic bile acid, during the peri-transplant period has significantly contributed to improved outcomes after HCT by reducing hepatic complications and severe acute GVHD, thus improving survival [39]. VOD is a clinical syndrome characterized by ten-

Table 52.2 Acute infections in the early post-HCT patient

Sign/symptom	Pathogens	Differential diagnosis
Diarrhea	CMV colitis *Clostridium difficile* Adenovirus Enteric organisms (coxsackie A, rotavirus, norovirus, echovirus) *Cryptosporidium parvum* (rare)	Acute GVHD Medication side effect Mucosal injury due to conditioning chemotherapy/radiation
Pneumonia	Invasive aspergillosis Mucormycosis *Fusarium* species CMV Respiratory viruses Pneumocystis pneumonia Disseminated strongyloidiasis (rare) Disseminated toxoplasmosis (rare)	Pulmonary edema Engraftment syndrome Diffuse alveolar hemorrhage IPS Drug-/radiation-induced pneumonitis Aspiration
Hepatitis	Hepatitis viruses (HBV, HCV most common) CMV EBV HHV-6 Adenovirus Hepatosplenic candidiasis	Medication toxicity Acute GVHD Iron overload Sinusoidal obstruction syndrome
Encephalitis	HHV-6 HSV VZV CMV EBV JC polyomavirus West Nile virus Adenovirus Toxoplasmosis	Medications PRES
Hemorrhagic cystitis	BK polyomavirus (common) Adenovirus (less frequent) CMV, JC polyomavirus (rare)	Drug-induced cystitis (cyclophosphamide)

HCT hematopoietic cell transplantation, *CMV* cytomegalovirus, *GVHD* graft-versus-host disease, *IPS* idiopathic pneumonia syndrome, *EBV* Epstein-Barr virus, *HHV* human herpesvirus, *HSV* herpes simplex virus, *VZV*, varicella-zoster virus, *JC*, John Cunningham virus

der hepatomegaly, fluid retention/weight gain, and elevated serum bilirubin in patients who receive high-dose myeloablative conditioning chemotherapy and/or radiation. Patients receiving high-dose cyclophosphamide (120 mg/kg) and total body irradiation (TBI) over 14 Gy are at greatest risk. In addition, pre-existing liver disease poses a significant increased hazard of VOD. The clinical presentation includes enlarged liver size, right upper quadrant tenderness, weight gain, and renal sodium retention occurring 10–20 days after the start of a myeloablative conditioning regimen. Elevated bilirubin occurs 4–10 days after these preceding signs, and concurrent portal hypertension, thrombocytopenia, and renal and lung dysfunction usually accompany the overall presentation. Diagnosis is based on clinical presentation, although liver imaging and transvenous liver biopsy and/or measurement of hepatic venous pressure may provide additional guidance [40]. Treatment of VOD is largely supportive, including management of fluid and sodium balance and maximizing renal blood flow. Patients with multi-organ failure may require hemodialysis or mechanical ventilation. A phase III trial of defibrotide for treatment of severe VOD with multi-organ failure showed improvement in day 100 survival and response; however, outcomes in patients given defibrotide were compared to historical controls. The day 100 survival was 38% with defibrotide vs. 25% in controls ($p = 0.01$) [41].

Acute Pulmonary Complications After Allogeneic HCT

Respiratory failure is the most common reason for intensive care unit (ICU) admissions among HCT recipients, affecting approximately 60% of HCT recipients requiring ICU care [42]. Differential diagnoses of hypercapnic and hypoxemic respiratory failure in the HCT recipient are outlined in Table 52.3.

Idiopathic pneumonia syndrome (IPS) is a term used to describe a clinical syndrome including a spectrum of non-infectious diffuse lung injuries following HCT. Diagnosis requires evidence of widespread alveolar injury, absence of active lower respiratory tract infection, and absence of a cardiac, renal, or iatrogenic etiology [43, 44]. The incidence of IPS is reported to be 4–12% associated with high case fatality rates (60–86%) in the first 100–120 days fol-

Table 52.3 Differential diagnoses for acute respiratory failure in the HCT recipient

Hypercapneic respiratory failure	Hypoxemic respiratory failure
Neurologic causes Opiates and sedative medications Intracranial hemorrhage PRES (see below) Airway obstruction Underlying conditions (COPD, asthma) Laryngeal edema due to mucositis Early-onset acute bronchiolitis obliterans syndrome (BOS)	Infectious pneumonia Pulmonary edema from volume overload Congestive heart failure Pneumonitis caused by aspiration, infection, chemotherapy, or other medications Idiopathic pneumonia syndrome (includes peri-engraftment respiratory distress syndrome, acute fibrinous organizing pneumonia, delayed pulmonary toxicity syndrome, diffuse alveolar hemorrhage) Pulmonary embolism Pneumothorax Cryptogenic organizing pneumonia

PRES posterior reversible encephalopathy syndrome

lowing HCT [43, 45]. Pathological specimens will show diffuse alveolar damage and interstitial pneumonitis. Treatment includes high-dose steroids and use of TNF-alpha inhibitors such as etanercept. IPS is thought to be triggered by damage due to conditioning chemotherapy and radiation leading to endothelial injury and oxidative stress, propagated by host innate and donor T-cell immune reactions [46].

In a subset of patients with IPS, pulmonary hemorrhage or hemorrhagic alveolitis occurs. Diffuse alveolar hemorrhage (DAH) occurs in 5–12% of HCT recipients at a median time to onset of 12–19 days following both autologous and allogeneic HCTs [44]. This develops secondary due to diffuse alveolar damage from high-dose conditioning chemotherapy and/or radiation, exacerbated by thrombocytopenia. Infection may trigger this presentation as well. While radiographic features are often telling, the diagnosis is confirmed by bronchoalveolar lavage showing increasingly bloody return of lavage fluid. Treatment involves high-dose steroids (up to 2 mg/kg/day), platelet transfusions (to keep a threshold of at least 50,000), and supportive care. DAH is associated with high mortality rates, up to 60–100% [44]. A slow and prolonged steroid taper is advised following initial response to therapy.

Acute Renal Complications After Allogeneic HCT

Evaluation of the post-HCT patient with acute elevation in serum creatinine level requires a vigilant search for the underlying cause. Workup should include complete urinalysis and urine albumin/creatinine ratio, as well as workup for hemolysis, including complete blood count with blood smear, lactate dehydrogenase, haptoglobin, and serum level of calcineurin inhibitor (if applicable). Opportunistic viral infections such as BK virus and adenovirus may impact renal function or cause viral nephropathy and should be tested in the serum. Kidney ultrasound should also be considered where clinically indicated.

Transplantation-Associated Thrombotic Microangiopathy (TMA)

The presence of renal dysfunction, microangiopathic hemolytic anemia, elevated lactate dehydrogenase, and negative workup for immune-mediated hemolysis (negative direct and indirect Coombs tests), associated with neurologic dysfunction points toward a clinical diagnosis of TMA [47]. Guidelines propose that concurrent renal and neurologic dysfunction and defined schistocyte count are not required for TMA diagnosis [48]. There is no defined or effective treatment. Discontinuation of the use of calcineurin inhibitors and replacement with other methods of GVHD prophylaxis, such as sirolimus or mycophenolate mofetil, can be considered but are not proven strategies. Posttransplant considerations such as graft-versus-host disease (described below) may limit options for a switch in immunosuppressive treatment. Other therapies that have been investigated include plasma exchange with or without rituximab. Patients with elevation in plasma levels of C5b-9 may benefit from therapy with eculizumab, although clinical trials have shown mixed results [49, 50].

Acute Neurologic Complications After Allogeneic HCT

Chemotherapy used as part of the conditioning regimen prior to infusion of donor stem cells, as well as the immunosuppressive medications used for prevention of GVHD, is associated with a variety of neurologic complications. Among these, calcineurin inhibitors (cyclosporine and tacrolimus) are most commonly used and are associated with tremors, seizures, and posterior reversible encephalopathy syndrome (PRES). PRES is characterized by rapidly evolving (over hours to days) symptoms, including headache, altered consciousness, visual disturbances, and seizures [51]. Elevated serum levels of immunosuppressive medications are not related to the onset of neurologic symptoms [52]. Less common side effects of tacrolimus include brachial plexopathy, optic neuropathy, and hearing loss; cyclosporine has been associated with pseudotumor cerebri [53]. Other possible neurologic complications of chemotherapy agents commonly used in conditioning for allogeneic HCT are summarized in Table 52.4. In addition, prophylactic antiviral medications (e.g., acyclovir) and antibiotics frequently used in this population (e.g., cefepime, imipenem) are associated with risk of seizure. Cefepime and acyclovir may cause encephalopathy as well. Voriconazole commonly causes visual hallucinations in patients who take this for prophylaxis or treatment of invasive fungal infection in the peritransplant period.

Table 52.4 Neurologic complications of drugs commonly used in allogeneic HCT conditioning regimens

Drug	Neurologic complication
Busulfan Melphalan Cytarabine	Seizure
Cyclophosphamide Fludarabine Melphalan	Posterior reversible encephalopathy syndrome
Cytarabine	Cerebellar dysfunction
Cytarabine Thiotepa	Lymphocytic meningitis
Alemtuzumab Rituximab Fludarabine	PML (progressive multifocal leukoencephalopathy)

In addition to drug-induced neurologic complications, pancytopenia following conditioning chemotherapy increases the risk of intracranial bleeding, such as subdural hematoma and intraparenchymal hemorrhage. Neutropenia and immune compromise lead to increased risk of opportunistic CNS infections, including viral encephalitis from herpes simplex, Epstein-Barr virus, varicella-zoster virus, CMV, and HHV-6. Other etiologies may include fungal (*Aspergillus*, *Rhizopus*, *Candida* spp.) and parasitic organisms (*Toxoplasma gondii*).

Acute GVHD

Acute graft-versus-host disease (aGVHD) is a frequent and potentially life-threatening complication that occurs within the first 3–4 months following allogeneic HCT. It is an inflammatory process mediated by immune-competent T cells contained in the donor graft that recognize tissues of the recipient as "foreign." The GI tract, liver, and skin are the primary organs involved. Despite prophylaxis with immunosuppressive agents, aGVHD requiring treatment occurs in approximately 50% of patients after an HLA-matched related donor HCT. The incidence and severity of aGVHD increase with a higher degree of HLA disparity between the donor and recipient. Manifestations of aGVHD are outlined in Table 52.5.

The diagnosis of acute GVHD is made clinically based on classic signs and symptoms occurring within the first several weeks to months of allogeneic HCT. However, the diagnosis is not always straightforward, and alternative diagnoses (e.g., drugs, infection, residual toxicities from preparative regimen, VOD) must be ruled out. Biopsy of the involved tissues (i.e., skin and/or GI mucosa) helps corroborate the diagnosis of GVHD. Due to the increase risk of bleeding, especially in the setting of expected posttransplant thrombocytopenia, liver biopsy is reserved for patients in whom the results would unequivocally affect clinical decision-making. The severity of aGVHD is determined by an assessment of the degree of involvement of the skin, liver, and GI tract (Table 52.6). This grading system should not be confused with histological grades sometimes noted in pathology reports from skin and GI mucosal biopsies.

Table 52.5 Clinical manifestations of acute graft-versus-host disease (GVHD)

Organ involvement	Clinical manifestation
Skin	Erythematous maculopapular rash, often initially involving the palms and soles. May progress to involve the entire body surface and may be pruritic and painful in severe cases. Bullae may form leading to desquamation
Liver	Cholestasis with or without frank jaundice. Cholestasis enzymes are comparatively more elevated than transaminases
Gastrointestinal	Upper tract: anorexia, nausea, and vomiting Lower tract: diarrhea. In severe cases, may contain blood and mucosa and may be accompanied by abdominal cramping and paralytic ileus Endoscopy: in mild cases, may only show edema and erythema. In more severe cases, may show hemorrhage and ulcerations

Table 52.6 Clinical organ staging and grading of acute graft-versus-host disease (GVHD)

Stage	Skin	Liver	Gastrointestinal (quantity of diarrhea)
1	Maculopapular rash <25% of body area	Bilirubin 2.0–3.0 mg/dL	500–1000 mL
2	Maculopapular rash 25–50% of body area	Bilirubin 3.1–6.0 mg/dL	1001–1500 mL
3	Generalized erythroderma	Bilirubin 6.1–15.0 mg/dL	>1500 mL
4	Generalized erythroderma with bullae and desquamation	Bilirubin >15.0 mg/dL	Severe abdominal pain with and without ileus
Grade	*Organ involvement*		
I	Stage 1 or 2 skin involvement; no liver or gut involvement		
II	Stage 1 to 3 skin involvement; grade 1 liver or gut involvement		
III	Stage 2 or 3 liver or gut involvement		
IV	Stage 4 skin liver or gut involvement		

aGVHD limited to the skin and involving less than 50% of body surface area can be easily managed with topical glucocorticoids alone. In more advanced cases, first-line treatment consists of systemic glucocorticoids while continuing the original immunosuppressive prophylaxis regimen. While a prednisone-equivalent dose of 2 mg/kg/day used to be the conventional starting dose for patients requiring systemic immunosuppressive therapy, a randomized trial has shown that lower initial doses (0.5–1.0 mg/kg/day) are safe and effective for patients who present with mild-to-moderate aGVHD [54]. Minimally absorbed oral glucocorticoids (beclomethasone dipropionate and budesonide) are typically used concurrently for GI aGVHD. There is no general consensus on treatment duration and taper rates once symptoms have resolved. We typically treat with systemic glucocorticoids for 7–10 days and then attempt a taper over 1–2 months, as tolerated.

Only ~50% of patients will have a long-term response to systemic glucocorticoids. Secondary immunosuppressive therapy should be considered for patients receiving systemic glucocorticoids who have *(i)* progressive symptoms in any organ after 3 days of treatment, *(ii)* persistent grade III symptoms after 1 week of treatment, or *(iii)* persistent grade II symptoms after 2 weeks of treatment [55]. Patients with

aGVHD resistant to treatment with glucocorticoids have a dismal long-term prognosis, with an overall survival likelihood of approximately 50% at 6 months. The oral Janus-activated kinase (JAK) 1/2 inhibitor, ruxolitinib, is only one FDA-approved agent for treatment of steroid-refractory aGVHD [56].

Patients receiving prolonged systemic immunosuppressive therapy are at an increased risk for infections; therefore, prophylaxis against fungal infections, HSV/VZV reactivation, and PJP should be instituted concurrently. In addition, weekly screening for CMV should be performed to detect early reactivation necessitating preemptive therapy. Patients with acute gut GVHD are at high risk for malnutrition. Maintaining even minimal oral caloric intake appears to have GI-protective effects and should be encouraged. If parenteral nutritional is needed, feeding solutions should be low in fiber, fat, and lactose. Complete bowel rest and TPN may be indicated, at least temporarily, in severe cases of gut GVHD. Supportive measures with antidiarrheal agents, including loperamide or octreotide, may be considered.

Graft Failure

Graft failure (GF) is defined as the lack of engraftment following autologous or allogeneic HCT. GF is classified as primary when there is no evidence of engraftment within the first month after transplant, or secondary when there is a loss of a previously functioning graft. The incidence of GF is less than 3–5% in the autologous and matched allogeneic HCT but up to 10% in haploidentical or cord blood recipients. GF is associated with a dismal prognosis with an overall survival of only 20% at 3–5 years following its diagnosis [57]. Infections and bleeding are the primary causes of mortality. Table 52.7 lists risk factors for GF.

There is currently no standard approach to the management of GF. Common management strategies include ensuring therapeutic doses of immunosuppression, discontinuation of myelosuppressive drugs, administration of growth factors and thrombopoietin analogues (eltrombopag, romiplostim), donor lymphocyte infusion, and CD34+ cell boost. A second HCT is the only potential curative option for patients with GF [58, 59]. There is no definitive data guiding the choice of conditioning regimen and donor type. A nonmyeloablative or reduced-intensity conditioning regimen is typically used with the second HCT to avoid unacceptable cumulative toxicities. In patients with an immune-mediated graft rejection, the use of an alternative donor, whenever possible, is recommended [59].

Table 52.7 Risk factors of graft failure

Pretransplant	Peri-transplant	Posttransplant
HLA mismatch HLA antibodies ABO mismatch Iron overload Transfusion history Underlying diseases (nonmalignant disease, myelofibrosis, advanced disease) Splenomegaly	Graft sources (cord blood/bone marrow stem cell source, and haploidentical donor) T-cell depletion graft manipulation Reduced-intensity conditioning Low CD34+ cell count	Viral infections GVHD Drug toxicity

HLA human leukocyte antigen, *GVHD* graft-versus-host disease

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Toxicities of Novel Antineoplastic Therapies

53

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Introduction

Many novel cancer therapy agents, altogether about a hundred, have been approved by the US Food and Drug Administration (FDA) between 2011 and 2020 for hematologic malignancies (Table 53.1) and solid tumors (Table 53.2). These new treatments offer improved clinical outcomes and survival of cancer patients at the price of treatment-related adverse events. Thus, the emergence of new treatment-related adverse events and syndromes will present diagnostic and management challenges to emergency physicians when they provide care for the cancer patient.

Case Study

A 65-year-old man with metastatic melanoma presents to the emergency department (ED) with the chief complaints of general weakness and confusion. He is not known to have brain metastasis, and his magnetic resonance imaging (MRI) of the brain did not show any metastatic disease 1 month prior to ED presentation. For his melanoma, he is not on cytotoxic chemotherapy and received his fourth dose of immunotherapy with ipilimumab 1 week ago. He complains of progressive general weakness, and he felt too weak to get out of bed without assistance for the past 2 days. He has lost his appetite and has nausea for about 3 days, resulting in decreased oral intake. He is lethargic and disoriented but without focal neurological complaints. His review of systems reveals symptoms of mild headache and constipation.

His vital signs are normal except for orthostatic hypotension. His physician examination is within normal limits except for disorientation to time, lack of concentration, inability to perform serial-7 subtraction, and lethargy. Laboratory testing reveals the following: serum sodium 128 mEq/L, blood urea nitrogen 35 mg/dL, creatinine 1.1 mg/dL, and glucose 68 mg/dL. The rest of the comprehensive metabolic panel and complete blood count with differential are normal.

Further testing in the ED shows that cortisol level is 2.7 μg/dL, thyrotropin 0.06 mIU/L, and free thyroxine 0.6 ng/dL. MRI of the sella reveals a slightly enlarged pituitary gland (1.2 cm in height, 1.1 cm in anterior-posterior dimension, and 1 cm in width). The dome of the mass is slightly indenting the inferior aspect of the optic chiasm.

The patient is diagnosed with adrenal insufficiency and central hypothyroidism due to ipilimumab-induced hypophysitis. The patient is hospitalized for further evaluation and management of this immune-related adverse effect (irAE). Endocrinology service is consulted; dynamic testing with low-dose cosyntropin stimulation test and measurements of adrenotropin corroborates central hypoadrenalism. Testing of other pituitary axes reveals panhypopituitarism.

General Approach

To appropriately and promptly diagnose and manage these toxicities, emergency physicians should be familiar with the array of adverse effect of these cancer therapies. This chapter will summarize the recent therapeutic advances in the field of oncologic and provide a reference for emergency physicians dealing with adverse events that are caused by these new agents and may present as oncologic emergencies. Some of these presentations can mimic sepsis, and we propose an algorithm to guide emergency providers in their approach to these complications (Fig. 53.1), linking to existing diagnostic guidelines.

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Table 53.1 Novel drugs approved after 2010 for hematologic malignancies and their associated adverse events

Generic name	Brand name	FDA approval date	Mechanism of action	Indication	Comments	Adverse events
Chimeric antigen receptor-T-cells						
Tisagenlecleucel	KYMRIAH	08/30/17	CD19-directed genetically modified autologous T-cell immunotherapy	ALL	Patients with ALL up to 25 years	CNS events Cytokine release syndrome Hypogammaglobulinemia Infections, pancytopenia
				LBCL	Relapsed or refractory LBCL	CNS events Cytokine release syndrome Hypogammaglobulinemia Infections, cytopenias
Axicabtagene ciloleucel	YESCARTA	10/18/17	CD19-directed genetically modified autologous T-cell immunotherapy	LBCL	Relapsed or refractory LBCL	CNS events Cytokine release syndrome Infections, cytopenias
Monoclonal antibodies against programmed cell death protein-1 (PD-1), an immune checkpoint molecule						
Pembrolizumab	KEYTRUDA	06/13/18	PD-1 humanized mouse mAb	PMBCL, cHL	Mediastinal LBCL	Immune-mediated adverse events (most common, musculoskeletal pain, infection, fatigue, cough, dyspnea, diarrhea, abdominal pain, nausea, headache; most serious, arrhythmia, myocardial infarction, pericardial effusion) Infusion-related reactions
Nivolumab	OPDIVO	05/17/16	PD-1 human IgG4 mAb	cHL		Immune-mediated adverse events (most common, rash, diarrhea, cough; most serious, pneumonia, pneumonitis, pyrexia, infusion reaction) Transplantation-related complications (GVHD) Hepatic veno-occlusive disease
Small molecule inhibitors						
Enasidenib	IDHIFA	08/01/17	IDH2 inhibitor	AML	Relapsed or refractory acute myeloid leukemia	Indirect hyperbilirubinemia Differentiation syndrome
Ivosidenib	TIBSOVO	07/20/18	IDH1 inhibitor	AML	Relapsed or refractory AML	QT prolongation Leukocytosis Differentiation syndrome
Midostaurin	RYDAPT	04/28/17	FLT3 inhibitor	AML	AML *FLT3* mutation-positive (*FLT3*+), advanced mastocytosis	Febrile neutropenia Mucositis, nausea, vomiting Headache Petechiae, epistaxis Upper respiratory tract infection
Ponatinib	ICLUSIG	12/17/12	BCR-ABL inhibitor	CML, ALL	CML, Philadelphia chromosome-positive ALL	Cardiac and arterial vascular occlusive events Arrhythmias, HF Pancreatitis, hepatotoxicity Reversible posterior leukoencephalopathy
Nilotinib	TASIGNA	03/22/18	BCR-ABL inhibitor	CML	Philadelphia chromosome-positive CML	QT prolongation, sudden death Myelosuppression Cardiac and arterial vascular occlusive events Pancreatitis and hepatotoxicity

Bosutinib	BOSULIF	09/04/12	BCR-ABL inhibitor	CML	Philadelphia chromosome-positive CML	Myelosuppression Diarrhea, pancreatitis, hepatotoxicity Cardiovascular events
Zanubrutinib	BRUKINSA	11/14/2019	BCR inhibitor	MCL		Myelosuppression Arrhythmias
Ibrutinib	IMBRUVICA	11/13/13	Irreversible inhibitor of Bruton tyrosine kinase (BTK)	MCL, CLL, WM		Cytopenias Hypertension
Acalabrutinib	CALQUENCE	10/31/17	Second-generation BTK inhibitor	MCL		Headache, diarrhea, fatigue, myalgia Neutropenia, anemia, pneumonia Cardiac adverse events
Idelalisib	ZYDELIG	07/23/14	Phosphatidylinositol 3-kinase δ inhibitor	CLL, NHL, SLL	Relapsed CLL	Serious hepatotoxicity Diarrhea, colitis, perforation Pneumonitis Myelosuppression, infections
Duvelisib	COPIKTRA	24/09/18	Phosphatidylinositol 3-kinase δ and γ (PI3K-δ, γ) inhibitor	CLL, SLL, FL	Refractory CLL, SLL, or FL	Nausea, diarrhea Pyrexia Cytopenias
Copanlisib	ALIQOPA	09/14/17	Pan-class I phosphoinositide 3-kinase (PI3K) inhibitor	FL	Relapsed FL	Hyperglycemia, hypertension, infections, neutropenia Noninfectious pneumonitis Severe cutaneous reactions
Belinostat	BELEODAQ	07/03/14	Deacetylase I and II inhibitor	PTCL	Relapsed/refractory PTCL	Myelosuppression, infections Thrombotic microangiopathy Thromboembolic events Renal and hepatic toxicity Pneumonitis Tumor lysis syndrome QT prolongation Reversible posterior leukoencephalopathy
Panobinostat lactate	FARYDAK	02/23/15	Pan-deacetylase inhibitor	MM		Cytopenias, peripheral neuropathy Cardiac ischemia, arrhythmias Severe diarrhea
Carfilzomib	KYPROLIS	07/20/12	Proteasome inhibitor	MM		Myelosuppression, infections Hepatic toxicity Tumor lysis syndrome HF, QT prolongation
Ixazomib citrate	NINLARO	11/20/15	Proteasome inhibitor	MM		Cytopenias, vomiting, diarrhea, constipation, neuropathy, peripheral edema, back pain
Venetoclax	VENCLEXTA	4/11/2016	BCL2 inhibitor	CLL, SLL		Tumor lysis syndrome Myelosuppression Autoimmune hemolytic anemia
Ruxolitinib	JAKAFI	11/16/11	JAK inhibitor	Myelofibrosis, PV		Myelosuppression, sepsis HF Herpes zoster infection

(continued)

Table 53.1 (continued)

Generic name	Brand name	FDA approval date	Mechanism of action	Indication	Comments	Adverse events
Fedratinib hydrochloride	INREBIC	8/16/2019	JAK2 inhibitor	Myelofibrosis		Serious and fatal encephalopathy, thiamine deficiency Anemia, thrombocytopenia Gastrointestinal, hepatic toxicity Amylase, lipase elevation
Omacetaxine mepesuccinate	SYNRIBO	10/26/12	BCR-ABL1 and Mcl-1 synthesis inhibitor	CML	CML after failure of two or more TKIs	Myelosuppression Glucose intolerance
Monoclonal antibodies against cell surface antigens						
Ofatumumab	ARZERRA	04/17/14	CD20 human mAb	CLL	Recurrent or progressive CLL	Reactivation of hepatitis B virus infection Progressive multifocal leukoencephalopathy Tumor lysis syndrome Infusion reaction Cytopenias
Obinutuzumab	GAZYVA	11/01/13	CD20 humanized mAb	CLL, FL		Febrile neutropenia, thrombocytopenia Infusion reactions
Daratumumab	DARZALEX	11/21/16	CD38 human IgG1k mAb	MM		Cytopenias, diarrhea, pneumonia
Elotuzumab	EMPLICITI	11/30/15	Signaling lymphocyte activation molecule family 7 (SLAMF7) humanized mAb	MM		Pyrexia, anemia, pneumonia, pulmonary embolism, acute renal failure, hepatotoxicity Infusion reactions Second primary malignancies
Mogamulizumab-kpkc	POTELIGEO	08/08/18	CC chemokine receptor 4 (CCR4) humanized mAb defucosylated at the Fc region to enhance antibody-mediated cellular cytotoxicity	MF		Rash, infusion reactions GVHD if allogenic transplantation within 50 days of treatment
Antibody-drug conjugates						
Inotuzumab ozogamicin	BESPONSA	08/17/17	CD22 humanized mAb covalently conjugated to N-acetyl-γ-calicheamicin dimethylhydrazide	ALL	Relapsed or refractory B-cell precursor ALL	Veno-occlusive disease (sinusoidal occlusion syndrome) Infusion reactions Thrombocytopenia, neutropenia QT prolongation
Gemtuzumab ozogamicin	MYLOTARG	09/01/17	CD33 humanized mAb covalently conjugated to N-acetyl-γ-calicheamicin dimethylhydrazide	AML	CD33-positive AML	Infection, bleeding, prolonged thrombocytopenia Veno-occlusive disease, transaminitis
Brentuximab vedotin	ADCETRIS	09/19/11	CD30 chimeric mAb covalently linked with cleavable linkers to 3–5 units of monomethyl auristatin E	T-cell lymphoma, cHL	Anaplastic large cell or other CD30-expressing T-cell lymphomas, relapsed or refractory Hodgkin lymphoma	Progressive multifocal leukoencephalopathy Peripheral neuropathy Myelosuppression

Immunotoxin						
Moxetumomab pasudotox-tdfk	LUMOXITI	09/13/18	CD22-directed cytotoxin	HCL	Relapsed or refractory HCL	Hemolytic uremic syndrome Capillary leak syndrome
Bi-specific T-cell engager						
Blinatumomab	BLINCYTO	13/3/14	CD19-/CD3-bi-specific mAb	ALL	B-cell precursor ALL	CNS events Cytokine release syndrome
Protein-based therapy						
Asparaginase *Erwinia chrysanthemi*	ERWINAZE	11/18/11	Cytotoxicity by catalyzing deamidation of asparagine	ALL	ALL with hypersensitivity to *E. coli*-derived asparaginase	Serious hypersensitivity Bleeding or thrombosis Hypertriglyceridemia, pancreatitis Hyperammonemia
Immunomodulatory agent with antineoplastic activity						
Pomalidomide	POMALYST	02/08/13	Angiogenesis inhibitor, TNF-α inhibitor	MM		Myelosuppression Tumor lysis syndrome Severe cutaneous reactions Birth defects, fetal death Thromboembolic events ILD, pneumonitis

FDA US Food and Drug Administration, *ALL* acute lymphoblastic leukemia, *LBCL* large B-cell lymphoma, *PMBCL* primary mediastinal large B-cell lymphoma, *cHL* classic Hodgkin lymphoma, *GVHD* graft-versus-host disease, *AML* acute myeloid leukemia, *CNS* central nervous system, *CML* chronic myeloid leukemia, *HF* heart failure, *MCL* mantle cell lymphoma, *CLL* chronic lymphocytic leukemia, *WM* Waldenstrom's macroglobulinemia, *NHL* non-Hodgkin lymphoma, *SLL* small lymphocytic lymphoma, *FL* follicular lymphoma, *PTCL* relapsed/refractory peripheral T-cell lymphoma, *MM* multiple myeloma, *MF* mycosis fungoides, *HCL* hairy cell lymphoma, *PV* polycythemia vera, *ILD* interstitial lung disease

Table 53.2 Novel drugs approved after 2010 for solid tumors and their associated adverse events

Generic name	Brand name	FDA approval date	Mechanism of action	Indication	Comments	Adverse events
Monoclonal antibodies against programmed cell death protein-1 (PD-1), an immune checkpoint molecule						
Pembrolizumab	KEYTRUDA	09/04/14	PD-1 humanized mouse mAb	Melanoma		Immune-mediated adverse events (most common, musculoskeletal pain, infection, fatigue, cough, dyspnea, diarrhea, abdominal pain, nausea, headache; most serious, arrhythmia, myocardial infarction, pericardial effusion) Infusion-related reactions
		10/02/15		NSCLC		
		11/23/15		Renal cell cancer		
		08/05/16		Head & neck cancer		
		05/18/17		Urothelial cancer		
		09/22/17		Gastric cancer		
		06/12/18		Cervical cancer	HCC	
		11/09/18		Liver cancer		
		12/19/18		Merkel cell cancer		
		06/18/19		SCLC		
		07/30/19		Esophageal cancer		
		09/17/19		Endometrial cancer		
Nivolumab	OPDIVO	12/22/14	PD-1 human IgG4 mAb	Melanoma		Immune-mediated adverse events (most common, rash, diarrhea, cough; most serious, pneumonia, pneumonitis, pyrexia, infusion reaction) Transplantation-related complications (GVHD) Hepatic veno-occlusive disease
		03/04/15		Lung cancer	NSCLC, SCLC	
		11/23/15		Renal cell cancer		
		11/10/16		Head & neck cancer		
		02/02/17		Urothelial cancer		
		08/01/17		Colorectal cancer		
		09/22/17		Liver cancer	HCC	
Atezolizumab	TECENTRIQ	05/18/16	PD-1 humanized IgG1 mAb	Urothelial cancer		Immune-mediated adverse events (most common, fatigue, rash, diarrhea, transaminitis, infection, renal dysfunction; most serious, myositis, colitis, adrenal insufficiency, pneumonitis, myocarditis) Infusion-related reactions
		10/18/16		Lung cancer	NSCLC	
		03/08/19		Breast cancer		
		03/18/19		Lung cancer	SCLC	
Cemiplimab-rwlc	LIBTAYO	09/28/18	PD-1 recombinant human IgG4 mAb	Cutaneous squamous cell carcinoma		Immune-mediated adverse events (most common, fatigue, rash, nausea; most serious, cellulitis, pneumonitis, pleural effusion, duodenal ulcer, colitis, hypercalcemia, hypophysitis) Infusion-related reactions
Monoclonal antibodies against programmed cell death ligand 1 (PD-L1), an immune checkpoint molecule						
Avelumab	BAVENCIO	03/23/17	PD-L1 human IgG1 mAb	Merkel cell carcinoma		Immune-mediated adverse events (most common, fatigue, rash, emesis, elevated lipase; most serious, pneumonitis, hepatotoxicity, adrenal insufficiency) Infusion-related reactions
		05/09/17		Urothelial cancer		
		05/14/19		Renal cell cancer		
Durvalumab	IMFINZI	05/01/17	PD-L1 human IgG1κ mAb	Urothelial cancer		Immune-mediated adverse events (most common, fatigue, pruritus; most serious, hepatotoxicity) Infusion-related reactions
		02/16/18		NSCLC		
Monoclonal antibodies against cytotoxic T lymphocyte-associated antigen 4 (CTLA4), an immune checkpoint molecule						
Ipilimumab	YERVOY	03/25/11	CTLA4 human mAb	Melanoma		Immune-mediated adverse events (most common, fatigue, rash; most serious, colitis, HLH) Infusion-related reactions
		16/4/18		Renal cell cancer		
		11/6/18		Colorectal cancer		

Small molecule inhibitors						
Vandetanib	VANDETANIB	04/06/11	VEGFR inhibitor	Thyroid cancer		QT prolongation Hypertension, HF Dermatologic toxicity Interstitial lung disease
Regorafenib	STIVARGA	10/27/12	VEGFR inhibitor	Colorectal cancer Advanced GIST tumor Liver cancer		Hypertension Serious hepatotoxicity Dermatologic toxicity Reversible posterior leukoencephalopathy
Axitinib	INLYTA	01/27/12	VEGFR inhibitor	Renal cell cancer		Hypertension, HF Dermatologic toxicity Thrombotic events
Erdafitinib	BALVERSA	04/12/19	Pan FGFR kinase inhibitor	Bladder cancer	Locally advanced or metastatic urothelial carcinoma with abnormal FGFR gene	Hyperphosphatemia, nausea, stomatitis, dry mouth Central serous retinopathy/retinal pigment epithelial detachment
Neratinib maleate	NERLYNX	07/17/17	Irreversible HER2 and EGFR inhibitor	Breast cancer		Gastrointestinal toxicity, diarrhea
Lenvatinib mesylate	LENVIMA	02/13/15	VEGFR inhibitor	Endometrial cancer Renal cell cancer Liver cancer Thyroid cancer	HCC	Hypertension, cardiac dysfunction, QT prolongation, arterial thromboembolic events Renal and liver toxicity Hemorrhagic events Reversible posterior leukoencephalopathy Palmoplantar erythrodysesthesia
Cabozantinib-s-malate	COMETRIQ CABOMETYX	11/29/12 04/25/16	RTK inhibitor	Thyroid cancer Renal cell cancer Liver cancer		Hypertensive crisis Hemorrhage, perforations, fistulas, wound complications Thrombotic events Diarrhea Osteonecrosis of the jaw Reversible posterior leukoencephalopathy Palmoplantar erythrodysesthesia
Alectinib	ALECENSA	12/11/15	ALK inhibitor	NSCLC	ALK-positive NSCLC	Hepatic and renal toxicity ILD/pneumonitis Bradycardia Myalgia and CPK elevation
Crizotinib	XALKORI	11/20/13	ALK inhibitor	NSCLC	ALK-positive or ROS1-positive NSCLC	Myelosuppression QT prolongation, bradycardia Liver and lung toxicity Ocular toxicity
Ceritinib	ZYKADIA	04/29/14	ALK inhibitor	NSCLC	ALK-positive NSCLC	QT prolongation, bradycardia Gastrointestinal, liver, lung, and ocular toxicity Pancreatitis

(continued)

Table 53.2 (continued)

Generic name	Brand name	FDA approval date	Mechanism of action	Indication	Comments	Adverse events
Brigatinib	ALUNBRIG	04/28/17	ALK inhibitor	NSCLC	ALK-positive NSCLC	ILD/pneumonitis Hypertension, bradycardia Myalgia and CPK elevation Visual disturbance Pancreatic enzymes elevation Hyperglycemia
Lorlatinib	LORBRENA	11/02/18	RTK, ALK, ROS1 inhibitor	NSCLC	ALK-positive or ROS1-positive NSCLC	Serious hepatotoxicity ILD/pneumonitis Atrioventricular block CNS disturbance Hyperlipidemia
Entrectinib	ROZLYTREK	08/15/19	Pan-TRK ROS1, ALK inhibitor	NSCLC Solid tumors with NTRK gene fusion	ROS1-positive NSCLC Solid tumors with NTRK gene fusion	Liver and renal toxicity CHF CNS and visual disturbance Skeletal fractures QT prolongation Hyperuricemia
Osimertinib mesylate	TAGRISSO	11/13/15	Mutant selective EGFR inhibitor	NSCLC	EGFR T790M mutation-positive NSCLC	ILD/pneumonitis QT prolongation Cardiomyopathy Diarrhea, rash
Dacomitinib	VIZIMPRO	09/27/18	Second-generation pan EGFR inhibitor	NSCLC	NSCLC with EGFR exon 19 del or exon 21 L858R substitution mutations	ILD/pneumonitis Diarrhea, rash
Afatinib	GILOTRIF	06/12/13	Pan-HER and EGFR inhibitor	NSCLC	NSCLC with EGFR exon 19 del or exon 21 L858R substitution mutations	ILD/pneumonitis Cardiovascular toxicity Gastrointestinal and liver toxicity Severe cutaneous reaction
Vemurafenib	ZELBORAF	08/17/11	BRAF inhibitor	Melanoma	Melanoma with BRAF V600E mutation	Liver and renal toxicity Pancreatitis QT prolongation Severe cutaneous reactions Cutaneous malignancies Radiation sensitization Severe hypersensitivity Dupuytren contracture, plantar fascial fibromatosis
Dabrafenib	TAFINLAR	05/29/13	BRAF inhibitor	Melanoma	Melanoma with BRAF V600E mutation	Severe cutaneous reactions New cutaneous malignancy Hemorrhage, febrile reaction Cardiomyopathy, QT prolongation ILD/pneumonitis Ocular toxicity Venous thromboembolism

Encorafenib	BRAFTOVI	06/27/18	RAF kinase inhibitor	Melanoma	Melanoma with BRAF V600E or V600K mutation	New primary malignancies Hemorrhage QT prolongation Gastrointestinal toxicity Uveitis, rash
Trametinib	MEKINIST	05/29/13	MEK1/2 inhibitor	Melanoma	Melanoma with BRAF V600E or V600K mutation	Severe cutaneous reactions New cutaneous malignancy Hemorrhage, febrile reaction Cardiomyopathy, QT prolongation ILD/pneumonitis Ocular toxicity Venous thromboembolism
Cobimetinib	COTELLIC	11/10/15	MEK1 inhibitor	Melanoma	Melanoma with BRAF V600E or V600K mutation	New primary malignancies Hemorrhage Cardiomyopathy Photosensitivity, serous retinopathy, retinal vein occlusion Hepatotoxicity Severe dermatologic reaction Rhabdomyolysis
Binimetinib	MEKTOVI	06/27/18	MEK1/2 inhibitor	Melanoma	Melanoma with BRAF V600E or V600K mutation	Cardiomyopathy Venous thromboembolism Serous retinopathy, retinal vein occlusion, uveitis ILD/pneumonitis Hepatotoxicity Rhabdomyolysis Hemorrhage
Pexidartinib	TULARIO	08/02/19	KIT, CSF1R, FLT3 inhibitor	Tenosynovial giant cell tumor		Serious and potentially fatal hepatotoxicity
Larotrectinib sulfate	VITRAKVI	11/26/18	TRK inhibitor	Solid tumors with NTRK gene fusion		Neurotoxicity Hepatotoxicity
Palbociclib	IBRANCE	02/03/15	CDK inhibitor	Breast cancer	HR-positive, HER2-negative breast cancer	Neutropenia Gastrointestinal toxicity
Ribociclib	KISQALI	03/13/17	CDK inhibitor	Breast cancer	HR-positive, HER2-negative breast cancer	QT prolongation Hepatobiliary toxicity Neutropenia
Abemaciclib	VERZENIO	09/28/17	CDK inhibitor	Breast cancer	HR-positive, HER2-negative breast cancer	Diarrhea, Hepatotoxicity Neutropenia Venous thromboembolism
Olaparib	LYNPARZA	12/19/14	PARP inhibitor	Breast cancer Ovarian cancer	BRCA-mutated ovarian and breast cancer	Myelosuppression Secondary MDS/AML Pneumonitis
Rucaparib camsylate	RUBRACA	12/19/16	PARP inhibitor	Ovarian, fallopian tube, or primary peritoneal cancer		Secondary MDS/AML

(continued)

Table 53.2 (continued)

Generic name	Brand name	FDA approval date	Mechanism of action	Indication	Comments	Adverse events
Niraparib tosylate monohydrate	ZEJULA	03/27/17	PARP inhibitor	Ovarian, fallopian tube, or primary peritoneal cancer		Secondary MDS/AML Myelosuppression Hypertensive crisis
Talazoparib tosylate	TALZENNA	10/16/18	PARP inhibitor	Breast cancer	BRCA-mutated, HER2-negative breast cancer	Secondary MDS/AML Myelosuppression
Alpelisib	PIQRAY	05/24/19	Phosphoinositide 3-kinase (PI3K) inhibitor	Breast cancer	HR-positive, HER2-negative, PIK3CA-mutated breast cancer	Severe hypersensitivity Severe cutaneous reactions Hyperglycemia, DKA Pneumonitis Severe diarrhea
Trifluridine and tipiracil hydrochloride	LONSURF	09/22/15	TFT and TPI inhibitor	Esophageal cancer Gastric cancer Colorectal cancer		Severe myelosuppression Gastrointestinal toxicity
Enzalutamide	XTANDI	08/31/12	Androgen receptor antagonist	Prostate cancer	CRPC	Ischemic cardiovascular events, hypertension Fractures and falls Posterior reversible encephalopathy, seizure
Apalutamide	ERLEADA	02/14/18	Androgen receptor antagonist	Prostate cancer	mCSPC, nmCRPC	Ischemic cardiovascular events Fractures and falls Seizure
Darolutamide	NUBEQA	07/30/19	Androgen receptor antagonist	Prostate cancer	nmCRPC	Fatigue, pain in extremity, rash
Vismodegib	ERIVEDGE	01/30/12	SMO antagonist	Basal cell carcinoma		Embryo-fetal death, severe birth defects Muscles spasms Gastrointestinal toxicity
Sonidegib	ODOMZO	07/24/15	SMO antagonist	Basal cell carcinoma		Embryo-fetal death, severe birth defects CPK elevation
Cytotoxic agents						
Irinotecan hydrochloride liposome	ONIVYDE	10/22/15	Liposomal formulation of irinotecan	Pancreatic cancer		Fatal neutropenic sepsis Severe diarrhea ILD Severe hypersensitivity
Trabectedin	YONDELIS	10/23/15	DNA binding and cross-linking	Soft tissue sarcoma		Neutropenic sepsis Rhabdomyolysis Hepatotoxicity Cardiomyopathy Extravasation with tissue necrosis

Monoclonal antibodies against cell surface antigens						
Pertuzumab	PERJETA	06/08/12	HER2 recombinant humanized IgG1 mAb	Breast cancer	HER2-positive breast cancer	Cardiotoxicity Infusion reaction Hypersensitivity Gastrointestinal toxicity
Ado-trastuzumab emtansine	KADCYLA	02/22/13	HER2 recombinant humanized IgG1 mAb	Breast cancer	HER2-positive breast cancer	Cardiotoxicity Hepatotoxicity Gastrointestinal toxicity Infusion reaction Hypersensitivity
Ramucirumab	CYRAMZA	12/12/14	VEGFR2 recombinant IgG1 mAb	NSCLC Gastric cancer Colorectal cancer Liver cancer		Infusion-related reaction Hypertension Hemorrhage Arterial thrombotic events Reversible posterior leukoencephalopathy Wound healing complications
Dinutuximab	UNITUXIN	03/10/15	GD2 mouse/human IgG1 mAb	Neuroblastoma		Infusion reactions, capillary leak syndrome, hypotension Neuropathic pain Ocular neuropathy Myelosuppression Electrolyte abnormalities Hemolytic uremic syndrome
Necitumumab	PORTRAZZA	11/24/15	EGFR human IgG1 mAb	NSCLC		Cardiopulmonary arrest and/or sudden death Hypomagnesemia Venous and arterial thromboembolic events Dermatologic toxicities Infusion reactions
Olaratumab	LARTRUVO	10/19/16	PDGFR human IgG1 mAb	Soft tissue sarcoma		Infusion reactions
Antibody-drug conjugates						
Fam-trastuzumab deruxtecan-nxki	ENHERTU	12/20/2019	Humanized anti-HER2 IgG1 mAb covalently linked to a topoisomerase inhibitor	Breast cancer		ILD, pneumonitis Neutropenia LV dysfunction
Enfortumab vedotin-ejfv	PADCEV	12/18/2019	Human IgG1 mAb directed against nectin-4, microtubule inhibitor conjugate	Refractory urothelial cancer		Hyperglycemia Peripheral neuropathy Ocular and skin disorders Infusion site extravasation
Recombinant fusion protein						
Ziv-aflibercept	ZALTRAP	09/03/12	VEGFR 1 and 2 binding attached to human IgG1	Colorectal cancer		Hemorrhage, GI perforations, fistulas Wound complications Hypertension Thrombotic events Diarrhea Reversible posterior leukoencephalopathy

(continued)

Table 53.2 (continued)

Generic name	Brand name	FDA approval date	Mechanism of action	Indication	Comments	Adverse events
Antiandrogen						
Abiraterone acetate	ZYTIGA	04/28/11	CYP17 inhibitor	Prostate cancer	mCRPC	Adrenocortical insufficiency Hepatotoxicity Mineralocorticoid excess Cardiovascular disease
Radioactive isotope						
Radium 223 dichloride	XOFIGO	05/15/13	Alpha particle-emitting isotope radium-223	Prostate cancer	CRPC	Risk from radiation exposure Myelosuppression Secondary malignancies
Radioconjugates						
Lutetium 177 dotatate	LUTATHERA	01/26/18	Radiolabeled somatostatin analog	Gastroenteropancreatic neuroendocrine tumors	GEP-NETs	Risk from radiation exposure Myelosuppression Secondary MDS/leukemia Renal and hepatic toxicity Neuroendocrine hormonal crisis
Oncolytic viruses						
Talimogene laherparepvec	IMLYGIC	10/27/15	Oncolytic HSV-1	Melanoma		Accidental exposure may lead to transmission and herpetic infection Herpetic infection Injection site complications Immune-mediated event Plasmacytoma at injection site

FDA US Food and Drug Administration, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *HCC* hepatocellular carcinoma, *FGFR* fibroblast growth factor receptor, *HER2* human epidermal growth factor receptor 2, *EGFR* epidermal growth factor receptor, *VEGFR2* vascular endothelial growth factor receptor 2, *RTK* receptor tyrosine kinase, *ALK* anaplastic lymphoma kinase, *ROS1* C-ros oncogene 1, *TRK* tropomyosin receptor kinases, *MEK* mitogen-activated protein kinase, *CSF1R* colony-stimulating factor-1 receptor, *FLT3* FMS-like tyrosine kinase 3, *CDK* cyclin-dependent kinase, *PARP* poly(ADP-ribose) polymerase, *CPK* creatine phosphokinase, *ILD* interstitial lung disease, *CNS* central nervous system, *CHF* congestive heart failure, *MDS* myelodysplastic syndrome, *mCSPC* metastatic castration-sensitive prostate cancer, *nmCRPC* nonmetastatic castration-resistant prostate cancer

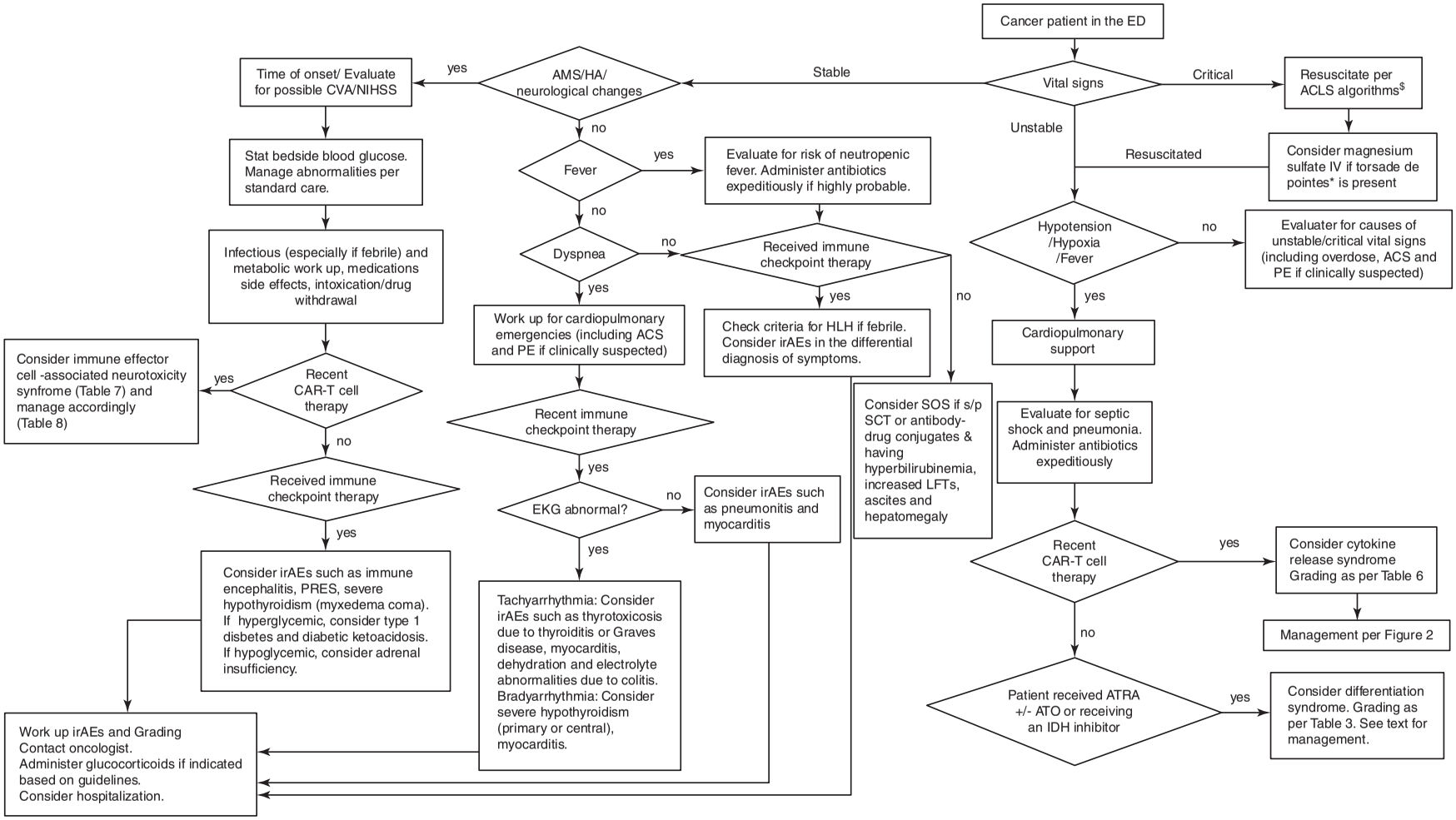

Fig. 53.1 Approach to evaluation of patients with hematologic malignancies treated with recently approved therapies in the emergency department. ACLS advanced cardiac life support, ACS acute coronary syndrome, AMS altered mental status, ATRA all-trans retinoic acid, ATO arsenic trioxide, CAR-T-cell chimeric antigen receptor-T-cell, CVA cerebrovascular accident, HA headache, NIHSS NIH stroke scale, HLH hemophagocytic lymphohistiocytosis, irAEs immune-related adverse events, LFTs liver function tests, PE pulmonary embolism, PRES posterior reversible encephalopathy syndrome, SCT stem cell transplantation, SOS sinusoidal occlusion syndrome. **Torsade de pointes* may be precipitated by QT-prolonging medications or hypomagnesemia. $When considering the H's in pulseless arrest, assess for hyperkalemia due to tumor lysis syndrome

"Familiar Scenes with New Actors"

Differentiation Syndrome

Differentiation syndrome (DS), also called the retinoic acid syndrome, was first recognized as a complication of treatment with all-*trans* retinoic acid and/or arsenic trioxide for acute promyelocytic leukemia. This life-threatening emergency is characterized by fever, hemodynamic instability, pulmonary infiltrates or effusions, edema, and renal failure within the first month of induction therapy in 25% (range: 2–48%) of acute promyelocytic leukemia cases [1–3]. In addition, DS can occur in a different clinical context: patients with relapsed or refractory acute myeloid leukemia who are receiving isocitrate dehydrogenase inhibitors (IDH inhibitors) [1]. Ivosidenib (IDH1 inhibitor) causes DS in 10.6% of patients [1] and enasidenib (IDH2 inhibitor) in 11.7% [1, 4]. These are lower rates than in acute promyelocytic leukemia. Classic DS has a bimodal distribution with peak incidence in the first and third weeks after initiation of induction therapy for acute promyelocytic leukemia, but IDH inhibitor-induced DS has a median onset time of 48 days (range 10–340 days) for enasidenib and 29 days (range 5–59 days) for ivosidenib [1, 5]. Thus, IDH inhibitor-induced DS may occur 1 week to 5 months after treatment initiation. Furthermore, IDH inhibitor-induced DS can recur after therapy interruption or dose escalation [4].

DS involves migration and infiltration of differentiated white blood cells into various organs, leading to endothelial activation and release of cytokines and vascular factors [1]. DS is a challenging clinical diagnosis because there are no specific laboratory tests or imaging modalities. Classic signs are dyspnea, unexplained fever, >5-kg weight gain (from fluid retention), unexplained hypotension, acute renal failure, pulmonary infiltrates, and pleural and/or pericardial effusion on imaging [2, 3]. DS grading is based on the number of classic signs and symptoms (Table 53.3). Because DS can mimic decompensated heart failure, pneumonia, and sepsis, emergency physicians should be aware of the clinical settings that raise suspicion of DS in order to promptly diagnose and manage DS. Early intervention and treatment with corticosteroids can reduce mortality from 30% to <1% [2, 3].

Table 53.3 Differentiation syndrome signs, symptoms, and grading [2, 4]

Signs and symptoms	Grading	
Bone pain	≤2 signs or symptoms	Mild
Dyspnea		
Fever		
Headache		
Hepatotoxicity	3 signs or symptoms	Moderate
Hypotension		
Leukocytosis		
Peripheral edema		
Pleuropericardial effusion	≥4 signs or symptoms	Severe
Pulmonary infiltrates		
Renal failure		
Weight gain >5 kg		

Elevated white blood cell count >5 × 10^9/L and serum creatinine level are associated with an increased risk of severe DS and mortality [2]. In the right clinical settings, DS should be treated as soon as suspected because delayed workup and management increases morbidity [1, 6]. The role of the emergency physician is critical for early diagnosis and timely management (including a timely hematology/oncologic consultation). The mainstay treatment is high-dose glucocorticoids (dexamethasone 10 mg/day) until symptom resolution [1, 3, 4]. The addition of broad-spectrum antibiotics is appropriate when sepsis is suspected because of the overlap with the signs and symptoms of DS. Uric acid must be checked, and hyperuricemia management is important [1, 2, 4]. For patients with renal failure, hemodialysis may be required, and for those without renal failure, fluid overload can be treated with diuretics [4]. In severe cases, oxygen supplementation, ventilatory and hemodynamic support, and admission to the intensive care unit may be required.

Infusion-Related Reactions

An infusion-related reaction is an adverse reaction to the infusion of a pharmacologic or biologic substance as defined in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) [7], and it occurs upon infusion or within a few hours after infusion of a drug (commonly a monoclonal antibody (mAb) and a biological) [8]. CTCAE provides a severity grading scale [9]. Many chemotherapy agents administered intravenously are associated with infusion-related reactions. Infusion reactions can be allergic (IgE-mediated) or anaphylactoid in nature (i.e., not truly allergic and non-IgE-mediated). Both types of reactions involve the immune system and can have a similar clinical presentation: rash, urticaria, pruritus, bronchospasm, nausea, vomiting, abdominal pain, dizziness, headache, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, fever, hypotension, and tachycardia [10]. This combination of signs and symptoms is related to cytokine release within the first few hours after administration. Infusion-related reactions can manifest hours after the patient has left the outpatient infusion facility, requiring presentation to an ED for acute management [11]. Severe reactions require prompt evaluation and management to avoid severe morbidity and mortality [10]. Unlike hypersensitivity reactions, symptoms of these reactions seem to become less intense with subsequent doses.

For the new biologic drugs (see Tables 53.1 and 53.2), infusion-related reactions are usually mild to moderate

(grade ≤2). The incidence rates of infusion-related reactions appear to vary among these agents. Blinatumomab is a bispecific T-cell engaging molecule that is administered as a continuous infusion for several weeks for patients with acute lymphoblastic leukemia. Infusion-related reactions occur in about half of these patients, but only 0.5% are serious reactions [11, 12]. Ofatumumab and obinutuzumab are associated with around 60% incidence [11, 13]; daratumumab and elotuzumab, 40–50% [11, 14]; mogamulizumab, 34% [15]; brentuximab, 11–15%; inotuzumab ozogamicin, 10% [16]; and pembrolizumab and nivolumab, 1–5% [11].

Management depends on the severity. In the emergency setting, infusion of the triggering agent should be stopped if not already completed. Treatment includes corticosteroids, antihistamines (both H1 and H2 receptor antagonists), and epinephrine (subcutaneous or intramuscular anaphylaxis doses). Stabilize the respiratory status and support hemodynamics according to resuscitation guidelines [11, 17].

QT Prolongation

Acquired QT prolongation on an electrocardiogram is a potentially serious adverse effect of medication. A long QT interval increases the risk for polymorphic ventricular tachycardia (*torsade de pointes*) and sudden death. The FDA recommends to correct the QT interval using the Fridericia formula (QTc), and cautions against a QTc >450 ms, and especially if >500 ms [18]. QT prolongation is most commonly associated with electrolyte derangements (especially hypomagnesemia and hypokalemia in cancer patients), heart disease, certain antiarrhythmic agents, antiemetic drugs (e.g., ondansetron), antibiotics (e.g., ciprofloxacin), antipsychotics, and antidepressants [19]. It is also associated with multiple drugs used for treatment of malignancies and cancer-associated symptoms and complications [20]. Several new drugs (ivosidenib, nilotinib, belinostat, carfilzomib, and inotuzumab ozogamicin) for hematologic malignancies have QT-prolonging side effects (see Table 53.1) and quite a number (vandetanib, lenvatinib, crizotinib, ceritinib, entrectinib, osimertinib, vemurafenib, dabrafenib, encorafenib, trametinib, and ribociclib) for solid tumors (see Table 53.2).

In general, a thorough medical history (including current use of QT-prolonging medications), physical examination, and electrocardiogram should be obtained for ED patients taking these novel agents who have significant electrolyte abnormalities or symptoms of palpitations, dizziness, or syncope. In many electronic medical record systems or medication prescribing systems, concurrent use of QT-prolonging drugs will trigger warning messages. Caution is advised when QT-prolonging drugs are used together. Vigilance should be maintained to avoid co-administration of QT-prolonging drugs in the ED. Management of significant QT prolongation starts with discontinuation of QT-prolonging agents, correction of electrolyte abnormalities, assessment of patient stability, and cardiologist consultation when deemed necessary. In the setting of cardiac arrest, resuscitation and treatment of arrhythmias are guided by the advanced cardiac life support (ACLS) protocols [9], keeping in mind that intravenous magnesium sulfate would be indicated for *torsade de pointes*.

Sinusoidal Occlusion Syndrome

Sinusoidal occlusion syndrome (SOS), also called hepatic veno-occlusive disease (HVOD), is caused by a prothrombotic hypofibrinolytic state causing obliterative terminal venulitis in the liver. SOS is a serious emergency that happens in 8–14% of patients during the first month after hematopoietic stem cell transplantation. Antibody-drug conjugates, gemtuzumab ozogamicin and inotuzumab ozogamicin (see Table 53.1) are humanized anti-CD33 and anti-CD22 mAb, respectively, conjugated to a potent DNA-binding cytotoxic antibiotic ozogamicin (a derivative of calicheamicin) [21]. With these new drugs, SOS occurs in about 9% of patients with acute myeloid leukemia who receive gemtuzumab ozogamicin [22–24], around 1% in patients with relapsed or refractory B-cell non-Hodgkin lymphoma who receive inotuzumab ozogamicin, and as high as 13% in patients with relapsed or refractory acute lymphoblastic leukemia who receive inotuzumab ozogamicin [25, 26]. The triad of jaundice, hepatomegaly, and ascites should raise suspicion of SOS in these clinical settings.

The clinical presentation typically includes hyperbilirubinemia, elevated liver enzyme level, weight gain, ascites, and tender hepatomegaly. The differential diagnosis includes graft-versus-host disease, Budd-Chiari syndrome, congestive heart failure, medication toxicity, viral hepatitis, and sepsis. Grading is based on clinical findings, such as bilirubin level, liver enzyme levels, weight gain due to fluid retention, increased serum creatinine, and rate of progression (Table 53.4) [27]. With multi-organ failure, 80% of patients may die.

Table 53.4 Clinical grading of sinusoidal obstruction syndrome [27]

Grading criteria	Mild	Moderate	Severe
Total bilirubin, mg/dL	<5	5–8	>8
Liver enzymes (AST, ALT)	<3× ULN	3–8× ULN	>8× ULN
Serum creatinine	Normal	<2× ULN	>2× ULN
Weight above baseline	<2%	2–5%	>5%
Rate of clinical progression	Slow (6–7 days)	Moderate (4–5 days)	Fast (2–3 days)

AST aspartate transferase, *ALT* alanine transferase, *ULN* upper limit of normal

Treatment of SOS is mainly supportive. The main challenge for emergency physicians is fluid management, because intravascular volume needs to be optimized with crystalloids or colloid (e.g., albumin) solutions without overload to avoid hepatorenal syndrome. Colloid solutions may be indicated in the presence of hypoalbuminemia. Adequate oxygenation and maintenance of oxygen-carrying capacity by transfusion would help to minimize hepatic ischemic injury. Nephrotoxic and hepatotoxic drugs should be avoided. In moderate to severe cases, high-dose glucocorticoids (methylprednisolone 1 mg/kg/day intravenously) are indicated [28].

Emergency physicians must be aware of the potential for SOS after treatment with these antibody-drug conjugates or in patients who have recently undergone hematopoietic stem cell transplantation. Early suspicion of SOS is vital given the triad of jaundice, hepatomegaly, and ascites in the above clinical settings. The primary role of the emergency physician is to recognize and diagnose this syndrome and initiate glucocorticoid therapy along with a hematologist/oncologist consultation.

Tumor Lysis Syndrome from Venetoclax-Based Therapy

Tumor lysis syndrome is a well-known oncologic emergency, especially when the tumor/malignancy burden is high. Venetoclax, a BCL2 inhibitor used as a single agent or in combination with other targeted therapies (see Table 53.1), has shown an increase risk of tumor lysis syndrome [29].

Novel Adverse Effects of New Immunotherapy for Cancer

Immune-Related Adverse Events (irAEs)

Immunotherapy has emerged as an effective cancer treatment by enhancing the ability of immune cells to kill cancer cells [30]. Malignant cells can evade host immune surveillance by usurping immune checkpoint pathways. Immune checkpoints regulate the immune response to prevent hyperinflammation or autoimmunity [31–35]. mAbs that bind and block cytotoxic T lymphocyte-associated protein 4 (CTLA4), programmed cell death protein-1 (PD-1), and programmed cell death ligand 1 (PD-L1) are approved to treat many different cancers by "releasing the brakes" on T-cell activation. Immune checkpoint inhibitors are now used for many solid tumors and hematologic malignancies (see Tables 53.1 and 53.2).

Stimulating the immune system to fight cancer is a double-edged sword; it can cause autoimmunity, leading to many irAEs. The estimated incidence of irAEs of any severity/grade was about 30% for anti-PD-L1 and anti-PD-1 therapies, and 75% for anti-CTLA4 therapy [36]. Most irAEs affect the integumental, gastrointestinal, endocrine, pulmonary, and musculoskeletal systems. Serious renal, neurologic, and cardiac irAEs may also occur. Prompt investigation of symptoms is vital for timely diagnosis and management.

Emergency physicians are at the front line to deal with acute presentation of irAEs. Existing guidelines from various professional organizations (National Comprehensive Cancer Network [NCCN] [37], American Society of Clinical Oncologic [ASCO] [38], Society for Immunotherapy of Cancer [SITC] [39], and European Society for Medical Oncologic [ESMO] [40]) can provide a framework for management of irAEs.

In the ED setting, the medical history about ICI therapy and onset of symptoms may cue the investigation of potential irAEs, since the incidence of irAEs usually peaks around the fourth dose (12–16 weeks after initiation) [41]. However, irAEs can occur any time during treatment (from after a single dose [42] to a prolonged period [40] and even after treatment discontinuation [43–46]). Grading of the severity of irAEs is based on CTCAE, version 5.0 [7]. Table 53.5 compiles grading and grade-based treatment considerations in the ED for common irAEs.

Immunosuppression with a glucocorticoid is the primary treatment for clinically significant irAEs. Escalation to other immunosuppressants (e.g., infliximab for colitis [47] or mycophenolate mofetil for hepatitis [48]) may be required in steroid-refractory cases or when significant steroid-induced side effects occur. Emergency physicians will primarily be dealing with the decision to initiate first-line therapy with glucocorticoids, in collaboration with the primary oncologists [37–39]. The occurrence of irAEs and subsequent use of immunosuppressive therapy do not seem to affect cancer response rates or antitumor therapeutic activity [49, 50].

Cardiac irAEs Cardiac dysfunction induced by ICI results from damage by lymphocytic infiltration [51–55]; immune-mediated myocarditis may present in EDs as acute life-threatening events. The onset may be rapid and can lead to cardiac failure or dysrhythmias (including ventricular tachycardia or complete atrioventricular heart blocks) that are potentially fatal [51, 56, 57] (see Fig. 53.1). The incidence of cardiac dysfunction is not clear but is perhaps ≤1% [51, 52]. The acute management of cardiac irAEs basically follows the ACLS algorithms along with consideration for initiation of glucocorticoid therapy emergently and other considerations mentioned in Fig. 53.1. These patients will often need to be admitted for cardiac monitoring, and intensive care needs to be considered.

Endocrine irAEs Endocrine toxicities of ICIs manifest hormone deficiency or excess. The spectrum of clinical ill-

Table 53.5 Management of common irAEs based on grades in the emergency department* [37]

	Grade	1 (mild)	2 (moderate)	3 (severe)	4 (life-threatening)
	General guidance for grading	Mild or no symptoms	Limiting age-appropriate ADL	Medically significant; limiting self-care; need hospitalization	Urgent intervention needed to prevent death
General management[a]					
	Systemic corticosteroid		Prednisone equivalent (0.5–1 mg/kg/day)	Prednisone equivalent (1–2 mg/kg/day)	Prednisone equivalent (1–2 mg/kg/day)
	ED disposition	Discharge	Consider hospitalization	Hospitalize	Hospitalize; ICU if indicated
Specific considerations					
Maculopapular rash	Grading	<10% BSA	10–30% BSA	>30%BSA	
	Management	Antihistamine Emollient Topical corticosteroid (moderate potency)	Antihistamine; emollient; topical corticosteroid (high potency)	Urgent dermatology consult; topical corticosteroid (high potency)	
Pruritus	Grading	Mild and/or localized	Widespread and intermittent; skin changes from scratching	Widespread and constant; limiting self-care or sleep	
	Management	Topical corticosteroid (high potency)	Dermatology consult; antihistamine; topical corticosteroid (high potency); systemic corticosteroid not needed	Urgent dermatology consult; prednisone (0.5−1 mg/kg/day); GABA agonist (gabapentin/ pregabalin); measure serum IgE and histamine; if high, treat with omalizumab and antihistamine, respectively	
Blistering dermatological disorders (bullae)[b]	Grading			Skin sloughing <10% BSA in SJS	Skin sloughing 10–30% BSA in SJS or ≥30% BSA in TEN
	Management	Urgent dermatology consult; skin biopsy; topical corticosteroid (high potency)	Urgent dermatology consult; skin biopsy	Urgent dermatology & ophthalmology consults; skin biopsy	Urgent dermatology & ophthalmology consults; skin biopsy
Diarrhea/colitis	Grading	<4 BM/day above baseline & no symptoms of colitis	4–6 BM/day above baseline & colitis symptoms; no interference of ADL	>6 BM/day above baseline & colitis symptoms interference of ADL	>6 BM/day above baseline & colitis symptoms; interference of ADL
	Management	Hydration Antidiarrheals	Gastroenterology consult; CT scan of the abdomen/pelvis; r/o infection; inpatient supportive care; methylprednisolone (1 mg/kg/day IV)	Gastroenterology consult; CT scan of the abdomen/ pelvis; r/o infection; inpatient supportive care; methylprednisolone (2 mg/ kg/day IV)	Gastroenterology consult; CT scan of the abdomen/ pelvis; r/o infection; inpatient supportive care; methylprednisolone (2 mg/ kg/day IV)
Transaminitis (hepatic)	Grading	<3× ULN	35× ULN	>5−20× ULN	>20× ULN
	Management	Consider gastroenterology consult; r/o other causes (e.g., viral infection); discontinue hepatotoxic drugs	Consider gastroenterology consult; r/o other causes; discontinue hepatotoxic drugs; if bilirubin >1.5× ULN, hepatology consult, inpatient care, and prednisone equivalent (2 mg/kg/day)	Hepatology consult; r/o other causes; discontinue hepatotoxic drugs; prednisone equivalent (1−2 mg/kg/day); if bilirubin >1.5× ULN, prednisone equivalent (2 mg/kg/day)	Hepatology consult; r/o other causes; discontinue hepatotoxic drugs; methylprednisolone (2 mg/ kg/day IV)

(continued)

Table 53.5 (continued)

	Grade	1 (mild)	2 (moderate)	3 (severe)	4 (life-threatening)
Pneumonitis	Grading	No symptoms; confined to one lobe or <25% lung tissue	New and worsening symptoms	Involving all lobes or >50% lung tissue; limited self-care ADL	Life-threatening respiratory compromise
	Management	Pulse oximetry; chest imaging	Chest imaging; infection workup; consider bronchoscopy; supplemental oxygen; prednisone equivalent 1–2 mg/kg/day; empiric antibiotics	Chest imaging; infection workup; consider bronchoscopy; supplemental oxygen; prednisone equivalent 1–2 mg/kg/day; empiric antibiotics; pulmonary and infectious disease consults	Chest imaging; infection workup; consider bronchoscopy; supplemental oxygen/mechanical ventilation; fluid management; prednisone equivalent 1–2 mg/kg/day; empiric antibiotics; pulmonary and infectious disease consults

ADL activity of daily living, *BSA* body surface area, *ICU* intensive care unit, *SJS* Steven-Johnson syndrome, *TEN* toxic epidermal necrolysis, *ULN* upper limit of normal

[a]Generally applicable unless otherwise stated in special considerations below

[b]Steven-Johnson syndrome and toxic epidermal necrolysis are considered grade 3–4 bullous dermatitis

[*]The specific considerations shown in this table only cover some common irAEs. Please see the NCCN guidelines for more details

ness ranges from no symptoms to life-threatening endocrine emergencies [58–63] (e.g., thyroid storm [64], myxedema coma [65], diabetes ketoacidosis [66]) (see Fig. 53.1). ED visits for endocrine irAEs are often related to the thyroid, adrenal, and pituitary glands [67].

Hypophysitis often presents with nonspecific symptoms (headache, fatigue, and general weakness) that are often misattributed to malignancy, but failure to recognize and diagnose hypophysitis can lead to adrenal crisis [68–70]. Anorexia, nausea, weight loss, altered mental status, heat intolerance, and arthralgia are less common symptoms (10.5–21.1%) [68, 70, 71]. Visual defects, typically bitemporal hemianopsia, are rare because pituitary enlargement is mild [72]. Hyponatremia is a major electrolyte disorder associated with hypophysitis (47–56% of patients) [70, 71, 73]. Morbidity is predominantly related to central adrenal insufficiency [74], and can be fatal if undiagnosed and untreated. Initial treatment includes high-dose glucocorticoids (1 mg/kg methylprednisolone or equivalent) along with management of hyponatremia and hypotension. Without significant hyponatremia, intense headaches, or optic chiasm compression, physiologic replacement of glucocorticoids may be considered [75].

Primary adrenal insufficiency associated with ICIs is uncommon but may be underreported due to concurrent treatment with glucocorticoids for various reasons (including oncologic indications) or coexistence of central adrenal insufficiency [76]. Symptoms of adrenal crisis include hypotension, dehydration, and electrolyte abnormalities (especially hyponatremia), which require immediate intervention [74]. These symptoms can improve rapidly after starting corticosteroids [70]. Hydrocortisone and fludrocortisone are the mainstay treatments [77].

Most cases of primary thyroid irAE are related to thyroiditis [78]. Thyroiditis can manifest as subclinical or overt hyper- or hypothyroidism with a typical clinical course of transient hyperthyroidism (due to thyroid hormones released by gland destruction) followed by prolonged or permanent hypothyroidism [78, 79]. Graves' disease is an autoimmune hyperthyroidism in which autoantibodies stimulate the thyroid-stimulating hormone receptor. Thyrotoxic cancer patient may present to the ED for arrhythmia (e.g., atrial fibrillation, atrial flutter, and supraventricular tachycardia), but these patients with arrhythmia will also need to be evaluated to rule out myocarditis and pericarditis as concurrent irAEs contributing to arrhythmia. Thyrotoxicosis in thyroiditis is usually mild and manageable with β-blockers. However, in patients with Graves' disease, life-threatening thyroid storms can occur. Serum thyroid-stimulating antibodies and radionuclide thyroid scans can distinguish Graves' disease from thyroiditis. Graves' disease can be managed with β-blockers, antithyroid agents, and glucocorticoids [80] and, if needed, additional agents that block thyroid hormone release (e.g., potassium iodide, iopanoic acid, etc.) [81].

Immune thyroiditis may destroy enough thyroid tissue to cause primary hypothyroidism. Hypothyroid symptoms are often nonspecific [82]. Typical complaints include fatigue, lethargy, constipation, and cold intolerance. Unrecognized severe hypothyroidism may progress to myxedema coma. If a cancer patient with a history of immune checkpoint inhibitor therapy is in the ED with confusion, lethargy, bradycardia, hyponatremia, hypothermia, or constipation, severe hypothyroidism should be included in the differential diagnosis. Primary hypothyroidism is primarily managed with thyroid hormone replacement (e.g., levothyroxine) and supportive care [83].

New-onset type 1 diabetes mellitus may present with diabetic ketoacidosis in patients receiving ICI therapy [84–86],

and can occur even after one dose [42]. Although rare, diabetic ketoacidosis is potentially life-threatening and requires early recognition to initiate timely management including intravenous insulin infusion. Once stabilized, the patient requires long-term, if not lifelong, insulin therapy [87].

Gastrointestinal irAEs Patients treated with combination ICI therapy had incidence rates of 13.6%, 9.4%, and 9.2% for all-grade colitis, severe colitis, and severe diarrhea, respectively [88], which are higher rates than in monotherapy. Symptoms typically start 6–8 weeks after beginning ICI therapy [89, 90]. Corticosteroids are the primary treatment for gastrointestinal toxicities, with escalation to infliximab (mAb against tumor necrosis factor-alpha) for severe steroid-refractory colitis [37, 91–93]. Vedolizumab (mAb against α4β7 integrin) can be effective in steroid-refractory and infliximab-resistant enterocolitis [94, 95]. Immune-related hepatotoxicity is usually mild, presenting with no or a few nonspecific symptoms, but can be severe or even fatal in some cases [96]. Median time to hepatitis is typically 5–6 weeks after starting therapy but can occur months later. The differential diagnosis should be broad, and infectious hepatitis must be ruled out, especially when the patient also has fever. Autoimmune and drug-induced hepatitis can have similar presentations and may require further imaging studies and/or biopsy.

Hemophagocytic lymphohistiocytosis (HLH) HLH is also called macrophage activation syndrome (MAS) and is a life-threatening syndrome of hyperinflammation and progressive immune-mediated organ damage. ICI-induced HLH is rare. HLH is diagnosed by having ≥5 of the following criteria: (1) fever; (2) splenomegaly; (3) cytopenias (at least two lineages in complete blood counts); (4) hypertriglyceridemia or hypofibrinogenemia; (5) hemophagocytosis; (6) low natural killer cell function; (7) high serum ferritin; and (8) high-soluble IL-2 [97, 98]. Some of the diagnostic criteria will not be able to be assessed in the emergency center, but HLH should be considered in the differential diagnosis for cancer patients treated with ICIs presenting with fever, cytopenias, and signs of hyperinflammation [99] (see Fig. 53.1). Optimal treatment for HLH caused by immunotherapy is not known. In two case reports of HLH, one patient was treated with etoposide and dexamethasone [100], and the other was treated with prednisone and mycophenolate mofetil [101]. Morbidity and mortality due to HLH are partially attributed to delayed diagnosis, hence the vitally important role of the emergency physician in achieving early diagnosis and intervention with high-dose glucocorticoids.

Integumental irAEs IrAE involving the subcutaneous tissue is relatively rare, manifesting as varying forms of panniculitis [102–104]. In contrast, cutaneous irAEs are the most common irAEs, occurring in almost half of the patients receiving ICI therapy (Table 53.2). The majority are low grade, presenting within the first two cycles of therapy [105–109] with itching, erythema, rash, vesicles, or blisters [105, 108, 110, 111]. High-grade cutaneous irAEs occur in about 1–3% of patients, and require ICI therapy discontinuation and treatment with high-dose corticosteroids; GABA agonists (e.g., pregabalin or gabapentin) can be used for severe pruritus [38, 106, 110, 112]. Serious irAEs such as toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), and Steven-Johnson syndrome (SJS) can be fatal if not recognized and treated with high-dose corticosteroids as inpatient [37, 113–115].

Neurologic irAEs Low-grade and nonspecific neurologic symptoms, such as headache, dizziness, and sensory impairment, occur in 6–12% of patients receiving ICI combination or monotherapy [45, 116]. About 0.4–0.2% of patients treated with nivolumab and pembrolizumab have grade ≥3 irAEs [116, 117]; 0.3–0.8%, with ipilimumab [118, 119]; and up to 0.7%, with combination nivolumab and ipilimumab [120]. Overall, severe neurologic irAEs is rare (<1% of patients) [45], and usually happens within 1–7 weeks of therapy [121–123]. Seizures, confusion, ataxia, abnormal behavior, and altered consciousness warrant evaluation for encephalitis which occurs in 0.1–0.2% of patients [116, 124–127] (see Fig. 53.1). Emergent brain imaging with CT or MRI with and without contrast if available in the ED is indicated. Brain MRI is the imaging modality of choice for evaluation of neurologic irAEs. Non-enhanced MRI shows T2 hyperintensity in a quarter of cases [124, 125]. Dural thickening and meningeal enhancement may also be present [127]. If fever is present together with headache and/or meningeal signs, lumbar puncture with analysis of cerebrospinal fluid (CSF) in the ED is indicated to rule out meningitis. In neurologic irAEs, CSF analyses are consistent with lymphocytic meningitis (with mild to high pleocytosis, negative cultures, elevated protein, and cytopathology negative for malignancy).

Pulmonary irAEs The most frequently reported pulmonary symptoms are dyspnea (see Fig. 53.1) and nonproductive cough, with fever and chest pain reported less commonly [113, 128]. The presence of extrapulmonary irAEs is relatively common and should raise suspicion for coexisting pneumonitis [129] (see Table 53.2). Generally, new persistent cough or shortness of breath in patients receiving immune checkpoint inhibitors should prompt evaluation for pneumonitis. The incidence of pneumonitis is <1% but varied across trials of immune checkpoint inhibitors, perhaps because of underreporting of low-grade irAEs [130]. Nevertheless, pneumonitis is one of the most serious irAEs and can be fatal [74, 128, 131–133]. In patients with acute

pulmonary symptoms, infectious pneumonia is in the differential diagnosis, and empiric antibiotics coverage is indicated. Evaluation of suspected pneumonitis should include a CT scan of the chest and possibly, after admission from the ED, a bronchoalveolar lavage and lung biopsy [134]. Patients with grade ≥2 pneumonitis should start glucocorticoids, and be closely monitored [38]. Grade ≥3 pneumonitis requires inpatient care, evaluation to exclude infections, and probably consultation with pulmonary and infectious disease experts. Treatment with high-dose glucocorticoids (methylprednisolone, 1–2 mg/kg per day) should be initiated after discussion between the emergency physician and the oncologist, aiming to improve symptoms down to grade ≤1. Other immunosuppressant agents (e.g., infliximab, mycophenolate mofetil) or intravenous immunoglobulins are generally not used in the ED but may be used after admission if not improved after 48 hours.

Rheumatologic irAEs Rheumatic manifestations in cancer patients receiving immune checkpoint inhibitors are primarily arthritis, sicca symptoms (dry eyes, dry mouth, and parotid gland enlargement), and a polymyalgia-like syndrome [44, 135]. Among irAEs involving the musculoskeletal system, myositis can be serious. Myositis presents as proximal muscle weakness with an increase in serum muscle enzymes, with or without respiratory complaints [56, 136–148]. De novo cases have been reported [136, 149]. Necrotizing myositis is an emerging irAE [136, 146, 147, 150–152]. Several cases of concomitant myositis and myasthenia-like manifestations have been documented [136, 145]. Patients often present with "dropped heads," bilateral proximal limb muscle weakness, muscle pain, dyspnea, and, occasionally, fever. Of note, myositis can also be associated with unilateral or bilateral ptosis, ophthalmoparesis, and bulbar weakness. Creatine phosphokinase and aldolase levels—and sometimes cardiac troponins—are elevated. Further diagnostic evaluation may involve acetylcholine receptor antibody and myositis serum antibodies and electromyography, which usually occur after admission from the ED. The time from initiation of immunotherapy to development of myositis is variable, but in most cases, myositis occurs after a few infusions. Myositis can be life-threatening because of CO_2 retention and respiratory failure, and severe rhabdomyolysis may cause renal failure, electrolyte imbalance, and fatal arrhythmia; both requiring prompt diagnosis and management. When respiratory compromise is suspected (as prompted by shallow rapid breathing, dyspnea, low oxygen saturation, etc.), ventilatory status should be evaluated with arterial blood gas measurement, peak flows, and/or bedside pulmonary function tests (negative inspiratory force and vital capacity). If patient has respiratory failure, support with positive pressure ventilation or intubate for mechanical ventilation.

Chimeric Antigen Receptor (CAR)-T-Cell Therapy

Genetically engineered T-cells constitute a new class of therapeutic agents that offer hope for cure of malignancies. CD19-CAR-T-cell therapy was recently approved for the treatment of hematologic malignancies (see Table 53.1). CAR-T-cell therapy causes a new spectrum of acute toxic effects, which differ from those typically organ-specific irAEs associated with ICIs [30, 41, 153]. CAR-T-cell therapy-related toxicities are related to markedly increased circulating cytokines and manifest as two syndromes: cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) [12, 154, 155]. Occasionally, CRS can progress into HLH [12, 156, 157]. Glucocorticoids are immunosuppressive and effective in cellular therapy-induced CRS, ICANS, and HLH. Even though ED visits for these adverse events are rare as these patients are typically hospitalized during treatment, this landscape is likely to change as clinical experience with CAR-T-cell therapies increases and the duration of hospitalization will shorten.

Cytokine release syndrome Symptoms of CRS range from mild "flu-like" to life-threatening inflammatory responses (Table 53.6) [158]. Symptoms include high-grade fever, hypotension, hypoxia, fatigue, arthralgia, myalgia, rash, and/or multi-organ toxicity, which can also be symptoms of infection or sepsis (see Fig. 53.1). Serious CRS is characterized by hypotension and hyperpyrexia that can progress to an uninhibited systemic inflammatory response syndrome with circulatory shock requiring vasopressors, vascular leak, disseminated intravascular coagulation, and multi-organ system failure. Laboratory abnormalities include cytopenias, elevated creatinine, elevated liver enzymes, impaired coagulation, and elevated C-reactive protein level. The primary differential diagnosis is sepsis and septic shock, and empiric antibiotic coverage is recommended.

Respiratory involvement is common with CRS. Mild cases may involve tachypnea and cough but may progress to hypoxemia with bilateral pulmonary infiltrates on chest radiography. Some cases can progress to acute respiratory distress syndrome requiring mechanical ventilation. Moreover, patients with serious CRS often display vascular leak with peripheral and pulmonary edema and may have signs of cardiac dysfunction with reduced left ventricular contractility.

Management of CRS varies by grade [155, 159] (Fig. 53.2). For grade 1, supportive care should keep the patient well-hydrated using intravenous fluids with special attention to fluid balance to avoid pulmonary vascular congestion. For grade 2, hypotension should be treated promptly with intravenous crystalloid fluid. In patients who

Table 53.6 American Society for Blood and Marrow Transplantation cytokine release syndrome consensus grading[a]

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[b]	Present	Present	Present	Present
		Accompanied by		
Hypotension	None	Vasopressors not required *And/or*[c]	Vasopressor with/without vasopressin	Hypotension requiring multiple vasopressors any except vasopressin
Hypoxia	None	Hypoxia requiring low-flow nasal cannula[d] or blowby	Hypoxia requiring high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask	Hypoxia requiring positive pressure[e]

Adapted from Lee et al. [158], with permission from Elsevier
[a]Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence this CRS grading
[b]Fever as temperature ≥38 °C not attributable to other case
[c]CRS grade determined by the more severe event
[d]Low-flow nasal cannula as oxygen ≤6 L/min. High-flow nasal cannula is defined as oxygen >6 L/min
[e]CPAP, BiPAP, intubation, and mechanical ventilation

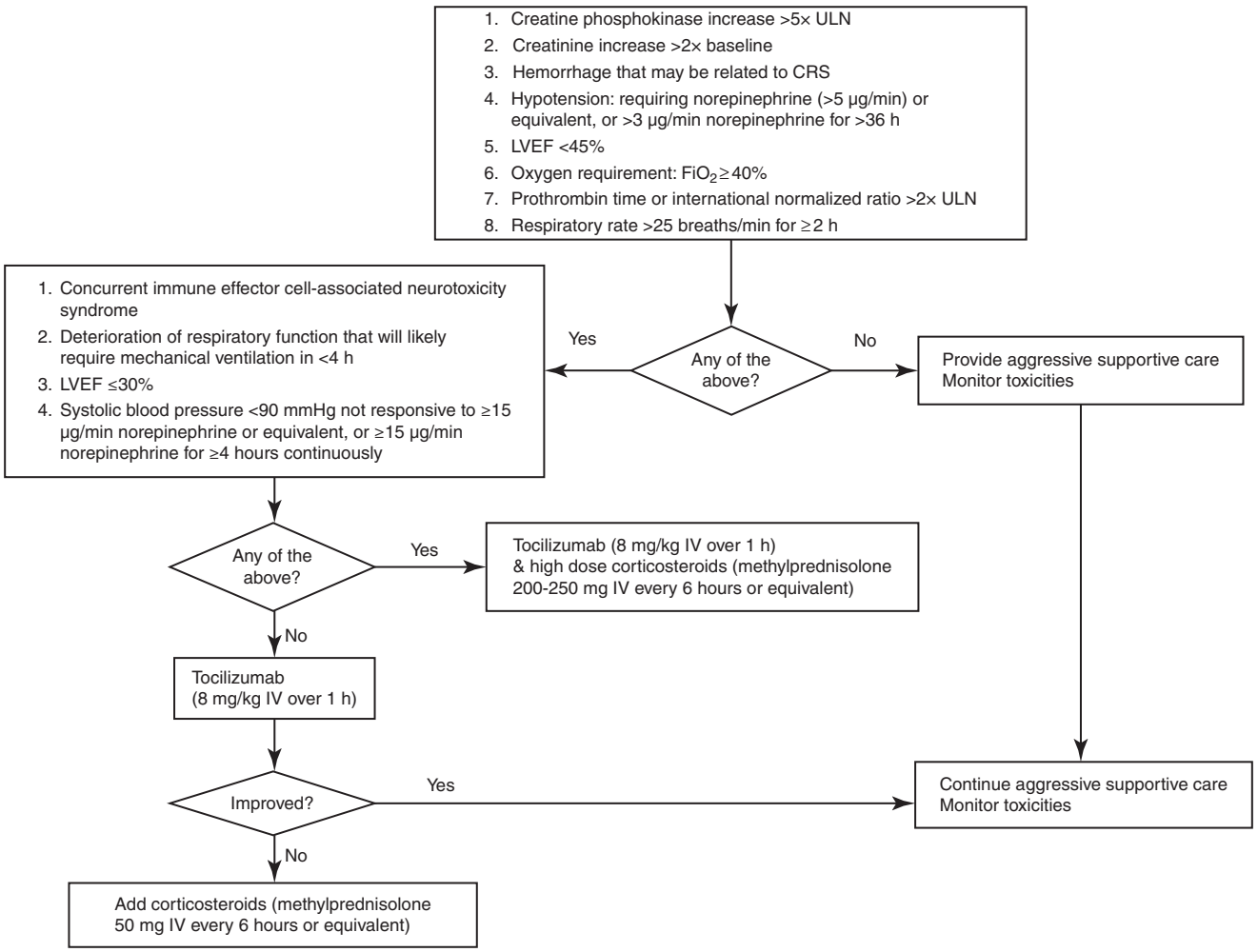

Fig. 53.2 Management algorithm for cytokine release syndrome (CRS). LVEF left ventricular ejection fraction, ULN upper limit of normal. (Adapted from Brudno and Kochenderfer [159] with permission from Elsevier)

are refractory to fluid boluses, management should include therapies that block IL-6 signaling (i.e., anti-IL-6 receptor antibody tocilizumab or anti-IL-6 antibody siltuximab) and glucocorticoids. For grade 3 or 4, emergently manage arrhythmias, hemodynamic shock, and respiratory compromise with antiarrhythmics, vasopressors, oxygen, and ventilation support, therapies that block IL-6 signaling and high-dose glucocorticoids. If possible, the emergency

team should be aware of all patients treated with CAR-T-cell therapy in the affiliated hospitals to facilitate prompt awareness of their CAR-T-cell therapy status when these patients present to the ED.

Immune effector cell-associated neurotoxicity syndrome Neurotoxicity is the second most serious adverse event following CAR-T-cell therapy [160]. Patients may develop a toxic encephalopathy (immune effector cell-associated encephalopathy [ICE]) with symptoms of confusion/delirium, problems with word retrieval, headache, somnolence, hallucinations, aphasia, hemiparesis, cranial nerve palsies, tremors, and, occasionally, seizures [77, 155–157, 161–166]. The pathophysiology of neurotoxicity is poorly understood, and is not strictly associated with the timing of CRS [155]. ICANS often starts shortly after CAR-T-cell infusion while the patients are still hospitalized, but some are delayed, and these patients may present to EDs with only neurologic symptoms.

The earliest signs of ICANS are decreased attention span, loss of language coherence, and impaired handwriting (Table 53.7). In severe cases (grade ≥3), seizures, motor weakness, incontinence, increased intracranial pressure, obtundation, papilledema, and cerebral edema may occur (see Fig. 53.1). The diagnosis of ICANS and evaluation may be guided by the need to obtain the information to use Table 53.7 to obtain the Immune Effector Cell-Associated Encephalopathy (ICE) score for the American Society for Blood and Marrow Transplantation Consensus Grading Scale. Emergent imaging study of the brain using CT or MRI is necessary. Emergent lumbar puncture for cerebrospinal fluid analysis would be indicated in the presence of mental status change and fever (e.g., concurrent CRS) to examine the differential diagnoses of meningitis and encephalitis.

Similar to CRS, the management of ICANS is also based on the toxicity grade (Table 53.8). For grade 1, supportive care is provided. Increasing the angle of the head of the bed to >30° may minimize the risk of aspiration and improve cerebral venous blood flow. Neurology consultation should be expeditiously requested to facilitate evaluation, including electroencephalogram, evaluation of intracranial pressure, and brain imaging studies. For grade 2, give high doses of glucocorticoids (dexamethasone 40 mg/day or methylprednisolone 1 g/day) until neurologic recovery [167]. For grades 3 and 4, in addition to high-dose glucocorticoids, control seizures and treat status epilepticus. Cerebral edema and increased intracranial pressure may require intensive care [168], and management with mechanical hyperventilation, acetazolamide, and/or mannitol [167]. In patients with concurrent neurotoxicity and CRS, treatment should include tocilizumab (8 mg/kg) and glucocorticoids until resolution of symptoms [167].

Table 53.7 Assessment of immune effector cell-associated neurotoxicity syndrome (ICANS)

Signs and symptoms	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (critical)
ICE[a]: orientation to year, month, city, hospital, 4 points; able to name three objects, 3 points; following simple commands, 1 point; able to write a sentence,1 point; or able to count backwards from 100 in 10s, 1 point	Able to perform 7–9 tasks	Able to perform 3–6 tasks	Able to perform 0–2 tasks	Obtunded and cannot perform tasks
Depressed level of consciousness	Spontaneous awakening	Awakening to voice	Awakening limited to tactile stimulus	Unarousable/requiring repeated or vigorous tactile stimuli for arousal Stupor/coma
Seizures	NA	NA	Clinical seizure focal or generalized resolving rapidly or nonconvulsive seizures on EEG responding to intervention	Life-threatening extended seizure (greater than 5 mins); or repeated clinical or electrical seizures with no return to baseline
Motor findings	NA	NA	NA	Deep focal weakness, e.g., hemiparesis/paraparesis
Increased intracranial pressure/cerebral edema	NA	NA	Focal/local edema on brain imaging	Diffuse cerebral edema on brain imaging; decerebrate or decorticate posturing; or abducens nerve palsy; papilledema; or Cushing triad

Adapted from Lee et al. [158], with permission from Elsevier
NA not applicable, *CRS* cytokine release syndrome, *EEG* electroencephalogram
[a]For Immune Effector Cell-Associated Encephalopathy (ICE) score, naming one object counts as one task, so the patient has the opportunity to perform three tasks

Table 53.8 Management of immune effector cell-associated neurotoxicity syndrome [167, 168]

Grade	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (critical)
Supportive care[a]	+	+	+	+
Neurology consult	+	+	+	+
Glucocorticoids	NA	Dexamethasone (40 mg/day) or methylprednisolone (1 g/day)	Dexamethasone (40 mg/day) or methylprednisolone (1 g/day)	Dexamethasone (40 mg/day) or methylprednisolone (1 g/day)
Tocilizumab	NA	NA	If concurrent with CRS, tocilizumab (8 mg/kg)	If concurrent with CRS, tocilizumab (8 mg/kg)
Seizure management	NA	NA	+	+
Cerebral edema and ICP management	NA	NA	Acetazolamide and/or mannitol	Mechanical hyperventilation, acetazolamide and/or mannitol
Critical care	NA	NA	+	+

CRS cytokine release syndrome, *ICP* increased intracranial pressure, *NA* not applicable
[a]Supportive care may include elevating the head of the bed to >30° to minimize the risk of aspiration and improve cerebral venous blood flow

Conclusion

Maintaining a fund of knowledge with updated information about the adverse effects of new cancer therapeutics is important. Knowing the timing, risk, and type of cancer treatment-induced toxicity will arm emergency physicians with the appropriate level of suspicion not to miss the correct diagnosis such that prompt management can improve patient outcomes. Rapid recognition and prompt initiation of appropriate evaluations and treatments are critical actions in the care of these oncologic emergencies.

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Fluorouracil or Capecitabine Overdose

54

Natalie R. Neumann and Christopher O. Hoyte

Case Study

A 62-year-old female recently diagnosed with metastatic colon cancer is brought to the emergency department (ED) by family members after revealing to them that she ingested her chemotherapeutic medication in a self-harm attempt. She reports to ED staff that she took several weeks' worth of her prescribed capecitabine. The ingestion was 8 hours ago, and the patient is currently asymptomatic. Her physical exam, EKG, and laboratory tests including a complete metabolic panel, complete blood count, and troponin are all reassuring. After discussing the case with the patient's oncologist and a toxicologist through the local poison center, the patient is administered uridine triacetate and admitted to the hospital for further observation and serial laboratory assessment.

History and Epidemiology

5-Fluorouracil (5-FU) is a mainstay of oncologic therapy. Its development is a classic example of rational drug design; it was created in the 1950s when researchers discovered that malignant cells utilized exogenous uracil, a pyrimidine base, more rapidly than nonmalignant cells to sustain ribonucleic acid (RNA) synthesis and thus tumor growth [1–4]. It is classified as a fluoropyrimidine derivative, its structure consisting of a pyrimidine bonded to a fluorine atom. 5-FU is, as the name suggests, a uracil analogue bonded to a fluorine atom in place of a hydrogen atom [3]. Other subsequently developed fluoropyrimidine derivatives that are used in oncologic therapy include capecitabine, doxifluridine, floxuridine, carmofur, and tegafur [5–9]. Fluoropyrimidines are themselves classified as antimetabolic agents. Antimetabolites are compounds that are similar enough to natural chemicals that they participate in physiologic biosynthetic pathways, but different enough that they also disrupt normal cell functions [5]. For the sake of simplicity, this chapter will focus largely on 5-FU and its prodrug, capecitabine. Cytotoxicity from these two fluoropyrimidines is attributed to their deleterious incorporation into RNA and deoxyribonucleic acid (DNA), and to their inhibition of thymidylate synthetase [1, 3, 4, 10] (Fig. 54.1).

Fluoropyrimidines may be administered as monotherapy or in combination with other chemotherapeutic agents. They are predominantly used for the treatment of gastrointestinal, breast, and head and neck cancers [1, 11, 12]. As of 2008, several hundred thousand patients in the United States received either 5-FU or capecitabine annually [13]. 5-FU is an intra-

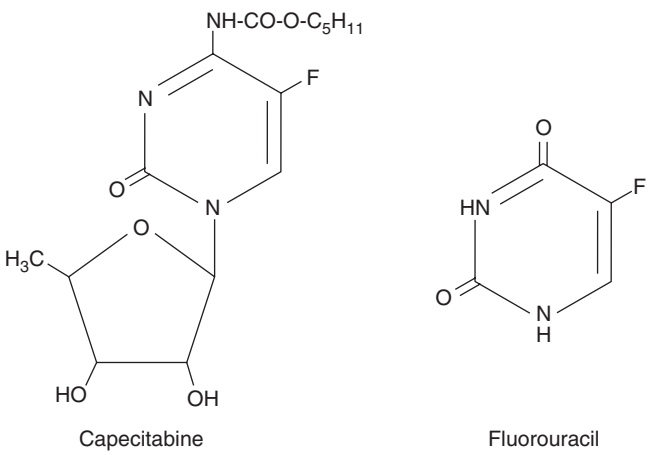

Fig. 54.1 Capecitabine and 5-fluorouracil chemical structures. (Adapted from Walko et al. [10], with permission Elsevier)

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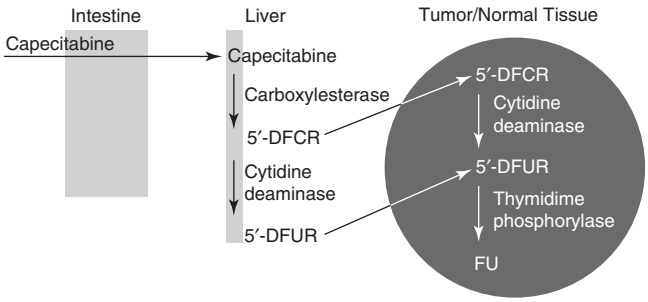

Fig. 54.2 Diagram of the conversion of the prodrug, capecitabine, to the active drug, 5-fluorouracil (5-FU). Capecitabine is first absorbed through the gastrointestinal tract and then converted by carboxylesterase in the liver to 5′-deoxy-5-fluorocytidine (5′-DFCR). Cytidine deaminase, present in both normal (e.g., liver) and malignant tissues, subsequently metabolizes 5′-DFCR to 5′-deoxy-5-fluorouridine (5′-DFUR). Thymidine phosphorylase, generally found in higher concentrations in tumor tissue compared to normal tissue, will finally convert 5′-DFUR to 5-FU. (Adapted from Walko et al. [10], with permission Elsevier)

venous (IV) formulation approved by the Food and Drug Administration (FDA) for the treatment of adenocarcinoma of the colon and rectum, breast, stomach, and pancreas [12]. It may be administered as a bolus or infusion [12]. Capecitabine is an oral prodrug which is metabolized intracellularly to 5-FU (Fig. 54.2) [10]. It was designed with the goal of creating a medication that delivered not only higher intra-tumor concentrations but greater convenience and tolerability for patients (i.e., fewer adverse effects) [10, 11, 14, 15]. According to the FDA, capecitabine is indicated for the treatment of metastatic colorectal cancer and metastatic breast cancer, and as an adjuvant treatment for colon cancer [11]. Survival and tumor response rates for both medications vary depending on the type of cancer being treated. Similarly, while adverse reactions to therapeutic administration of 5-FU and capecitabine are quite common, the exact rates vary depending on patient age, cancer type, means of administration, and whether the agents are used as monotherapy [11, 14, 16]. Studies differ, but it is estimated that between 10% and 40% of patients on 5-FU and capecitabine develop some form of severe or life-threatening toxicity, including mucositis, myelosuppression, neurotoxicity, cardiotoxicity, and hand-and-foot syndrome [16–25]. Mortality from 5-FU and capecitabine-induced toxicity is estimated at approximately 0.4–2% [16, 24, 26, 27]. A significant proportion of fatalities are thought to occur in the setting of therapeutic administration rather than acute overdose, and they are often attributed to genetic polymorphisms [18, 22, 28–31].

Pharmacodynamics

5-FU, as noted previously, is an analogue of uracil and an antimetabolite chemotherapeutic agent. It is hypothesized that 5-FU is taken up into cells via the same active transport system used to take up uracil [32]. Capecitabine, once ingested orally, is metabolized to 5-FU in liver and tumor cells. One enzyme critical to this conversion is cytidine deaminase (CDA) which is present in both normal and malignant tissues [11, 33, 34]. The third and final enzyme responsible for converting capecitabine to 5-FU is thymidine phosphorylase. Thymidine phosphorylase is thought to be found in much higher concentrations in tumor cells compared to normal tissues. Capecitabine's ability to localize to tumor cells and its improved side effect profile compared to 5-FU are attributed to this disparity in distribution [11, 34, 35].

Once 5-FU is present within the cell (after either direct uptake or metabolism of capecitabine), it is converted to three principal active metabolites which induce cytotoxicity by interfering with the function of thymidylate synthase (TS) and with the synthesis of RNA and DNA [1, 3]. These metabolites are fluorodeoxyuridine monophosphate (FdUMP), fluorouridine triphosphate (FUTP), and fluorodeoxyuridine triphosphate (FdUTP). Conversion of 5-FU to these active metabolites is accomplished in several steps and by multiple enzymes, including orotate phosphoribosyltransferase (OPRT) [1, 36]. Most administered 5-FU is not anabolized to an active metabolite, however. The enzyme dihydropyrimidine dehydrogenase (DPD) catabolizes approximately 80% to an inactive component which is largely excreted in urine [4, 37]. The aforementioned enzymes – CDA, TS, OPRT, and DPD – are relevant to understanding the toxicity of 5-FU as their genetic polymorphisms are associated with variable risk of developing clinical toxicity at therapeutic fluoropyrimidine dosing (Fig. 54.3) [1, 18, 30].

Thymidylate synthase is an enzyme that catalyzes the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), a nucleotide needed to synthesize DNA. Under physiologic conditions, thymidylate synthase uses 5,10-methylene tetrahydrofolate as a methyl donor to convert dUMP to dTMP. FdUMP, however, binds to TS with higher affinity than endogenous dUMP [38]. When present in the cell, FdUMP will form a stable but reversible ternary complex with thymidylate synthase (a dimer) and 5,10-methylene tetrahydrofolate [38–41]. Formation of this complex prevents binding of dUMP and so inhibits de novo dTMP production [1, 3]. This process is depicted in Fig. 54.4.

The exact means by which dTMP depletion leads to inhibition of DNA synthesis is not entirely known. Inadequate conversion of dUMP to dTMP is thought to create to a relative overabundance of dUTP. dUTP may then be incorporated inappropriately into DNA, resulting in strand damage and cell death [42–47]. FdUTP, another metabolite of 5-FU, can also be misincorporated into DNA, causing similar downstream effects [48–51]. In addition, decreased production of dTMP ultimately results in decreased dTTP availability which is thought to alter the concentrations of other

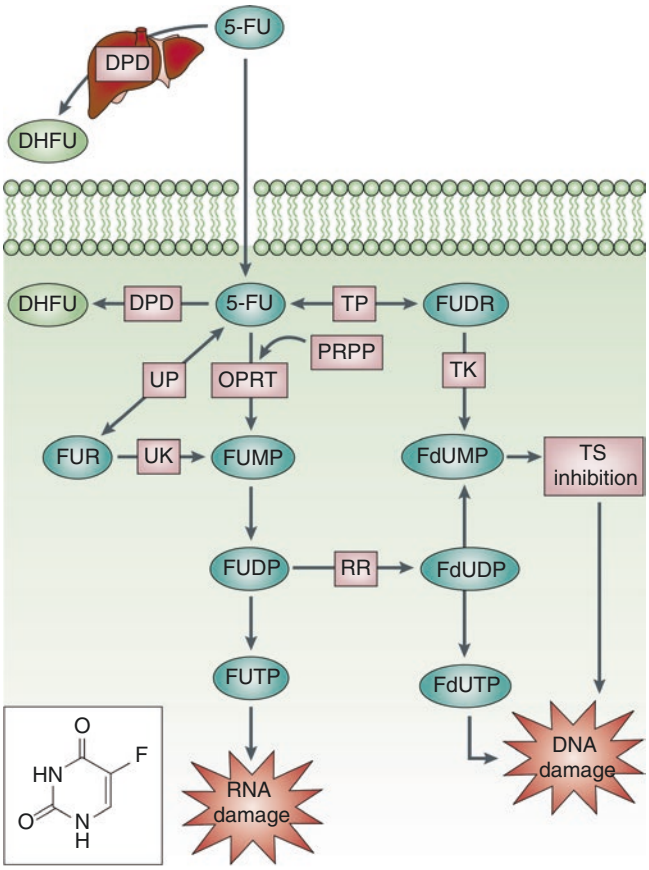

Fig. 54.3 A more detailed overview of the metabolism and mechanism of action of 5-FU. 5-FU is mostly catabolized by dihydropyrimidine dehydrogenase (DPD) to the inactive compound dihydrofluorouracil (DHFU). Much of this conversion takes place in the liver, but catabolism may also take place in other normal tissues and in tumor tissue. 5-FU may alternatively be metabolized to one of the three active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP), and fluorouridine triphosphate (FUTP). FUTP is formed in one of the two ways: 5-FU may be metabolized to fluorouridine monophosphate (FUMP) by orotate phosphoribosyltransferase (OPRT) with phosphoribosyl pyrophosphate (PRPP) acting as a cofactor. Alternatively, 5-FU may be metabolized by uridine phosphorylase (UP) to fluorouridine (FUR) and then to FUMP by uridine kinase (UK). FUMP, once formed, is phosphorylated to make fluorouridine diphosphate (FUDP) which may be subsequently phosphorylated to form FUTP. FUDP, rather than being converted to FUTP, can alternatively be metabolized to fluorodeoxyuridine diphosphate (FdUDP) by ribonucleotide reductase (RR). FdUDP may then be phosphorylated or dephosphorylated to form FdUTP or FdUMP, respectively. FdUMP is also formed if 5-FU, rather than being metabolized by UP or OPRT, is converted by thymidine phosphorylase (TP) to fluorodeoxyuridine (FUDR) and then to FdUMP by thymidylate kinase (TK). (From Longley et al. [1], with permission Springer Nature. © 2003 Nature Publishing Group)

deoxynucleotides. This imbalance is itself thought to damage DNA synthesis and repair [52, 53]. Finally, the abnormal ratio of dUTP to dTTP inhibits the action of uracil-DNA glycosylase, which as a nucleotide excision repair enzyme would normally remove inappropriate, uracil-based nucleotides from DNA strands [1, 48, 54]. Of note, thymidylate can be salvaged by thymidine kinase (TK). Increased intra-tumor thymidine kinase activity is a proposed mechanism of resistance to therapy (Fig. 54.4) [1, 55].

RNA disruption is achieved through multiple mechanisms as well, and is increasingly thought to be a significant contributor to cytotoxicity [47]. When present in the cell, FUTP, a 5-FU metabolite, may replace uridine triphosphate (UTP) and be incorporated into all forms of RNA [56, 57]. In this way it can disrupt the function of ribosomal RNA (rRNA), messenger RNA (mRNA), translational RNA (tRNA), and small nuclear RNA (snRNA) [3, 58–62]. Specifically, FUTP prevents the formation of mature rRNA by inhibiting pre-rRNA processing, disrupts the posttranslational modification of tRNA, inhibits polyadenylation of mRNA, and prevents snRNA-protein complex assembly [63–68]. Together these actions inhibit cellular function and may lead to cell death.

Pharmacokinetics

5-FU is administered intravenously. When given as a bolus, 5–20% is excreted unchanged in the urine over 6 hours. What remains is largely metabolized in normal and malignant tissues to active and inactive metabolites. The majority of 5-FU is catabolized (i.e., degraded to inactive compounds) by DPD in the liver and other tissues [3, 4, 12, 47, 69]. The degree to which 5-FU undergoes anabolism to metabolically active metabolites is thought to depend on the extent of catabolism [4, 37]. In other words, the more 5-FU is catabolized by DPD, the less is available to be converted to active metabolites. In general, less than 5% of 5-FU is anabolized [4].

Variable elimination half-lives and volumes of distribution have been reported for 5-FU; these range from 8 to 22 minutes and 14 to 54 liters, respectively [3, 12, 69–71]. The vast majority of 5-FU metabolites are excreted in the urine within 24 hours; approximately 2–3% undergo biliary excretion [37]. The half-lives of 5-FU's catabolites vary depending on the compound from 1 to 33 hours [3, 37]. Pharmacokinetic data regarding 5-FU continuous infusions is limited [3]. There are no specific recommendations for adjusting the dose of 5-FU in the setting of renal or hepatic dysfunction [3, 12, 72].

The bioavailability of IV 5-FU is by definition 100%. Tissue concentrations, however, vary significantly (up to a thousandfold difference) depending not only on the degree of hepatic metabolism but on whether or not the medication is administered as a bolus or as a slow infusion [71]. The oral bioavailability of 5-FU is highly variable and generally considered to be quite low given first-pass metabolism (one study reported a mean bioavailability of 28% with a range of 0–74%) [71, 73, 74]. Capecitabine also has rela-

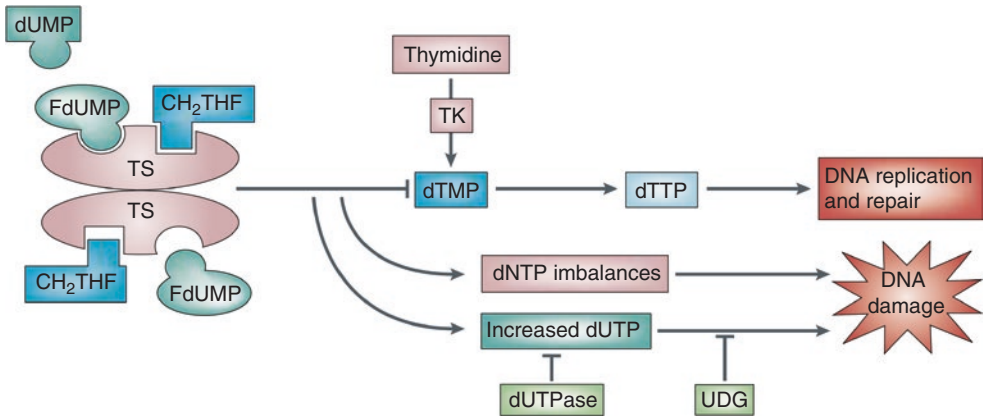

Fig. 54.4 Diagram of 5-FU's inhibition of thymidylate synthase (TS). TS uses 5,10-methylene tetrahydrofolate (CH_2THF) to catalyze the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). Fluorodeoxyuridine monophosphate (FdUMP), a 5-FU metabolite, interferes in this process by binding at the nucleotide-binding site of TS to form a stable ternary complex with TS and CH_2THF. When this complex forms, dUMP is unable to access the nucleotide-binding site, and dTMP synthesis is inhibited. This inhibition leads to deoxynucleotide (dNTP) pool imbalances and increased concentrations of dUTP, and DNA damage ensues. The degree of DNA damage caused by dUTP depends on pyrophosphatase dUTPase (dUTPase) and uracil-DNA glycosylase (UDG) concentrations. Thymidine kinase (TK) may salvage dTMP from thymidine. (From Longley et al. [1], with permission Springer Nature. © 2003 Nature Publishing Group)

tively low bioavailability. A study measuring the serum presence of 5′-deoxy-5-fluorouridine (the immediate precursor to 5-FU in the metabolism of capecitabine) determined that capecitabine had a mean oral bioavailability of 42% in cancer patients with normal hepatic function and 62% in those with hepatic dysfunction [75].

After oral dosing, capecitabine reaches peak serum concentrations at 1.5 hours; peak 5-FU concentrations occur at 2 hours [11]. Food consumption decreases both the rate and absolute amount of capecitabine absorption and delays by 1.5 hours the time to peak serum concentrations of both capecitabine and 5-FU. Less than 60% of capecitabine and its metabolites are protein bound, and this percentage is not dependent on drug concentrations [11, 76]. As noted previously, capecitabine undergoes three enzymatic steps to produce 5-FU; subsequent metabolism is identical to that of 5-FU [10, 11]. Mild to moderate hepatic dysfunction is not shown to have a clinically significant impact on the pharmacokinetics of capecitabine and its metabolites, but the FDA recommends that patients with hepatic dysfunction be monitored carefully on the medication [11, 75]. Similarly, no dose adjustment is initially required in the setting of mild renal dysfunction, but capecitabine is contraindicated in the setting of renal failure as defined by a creatinine clearance of less than 30 mL/min. The FDA also recommends that the dose be decreased in the setting of moderate renal impairment as defined by a creatinine clearance of 30–50 mL/min [11].

Of note, both 5-FU and capecitabine are found to decrease warfarin clearance, leading to an increase in INR [11, 77]. They are also known to increase phenytoin concentrations [11, 78]. Both warfarin and phenytoin are metabolized by CYP2C9 in the liver, suggesting that other drugs metabolized by this pathway should be closely monitored [10].

Toxicokinetics

Toxicity from 5-FU and capecitabine can result from intentional overdose, iatrogenic overdose, and therapeutic dosing [79–81]. Ma and colleagues, in one of the first studies exploring the use of uridine triacetate, noted that toxicity due to overdose was both rate and dose dependent. When three times the appropriate dose was administered, the observed outcome was death [28].

Toxicity in the setting of therapeutic drug administration is often associated with genetic variations that lead to abnormal enzyme activity [80, 81]. Genetic polymorphisms can lead to either excessive or deficient enzymatic activity. Polymorphisms associated with increased fluoropyrimidine toxicity are found in genes that code for the previously mentioned enzymes: DPD, CDA, and TS [18, 25, 29–31, 36, 82–86]. Other enzymes that are suspected of causing increased toxicity due to genetic polymorphisms include methylene tetrahydrofolate reductase (MTHFR) and orotate phosphoribosyltransferase (OPRT) [25, 30, 36].

Of these polymorphisms, DPD is the best studied. It is generally accepted that a significant proportion of patients who present with severe 5-FU- or capecitabine-induced toxicity (defined previously in studies as symptoms consistent with grade 3 or 4 toxicity) have a partial or complete DPD deficiency. Approximately 25–60% of patients with severe toxicity have a DPD deficiency, and such findings have led to recommendations that genetic testing be performed prior

to initiating fluoropyrimidine therapy [21, 30, 87–93]. Of note, it is estimated that only 2.7–5% of the general population (including those with cancer) has a partial DPD deficiency [93, 94]. Reduced DPD activity is not associated with increased age or abnormal liver function, but its relationship to gender is unclear, and rates of deficiency vary greatly between ethnicities [25, 93–95].

Risk factors that have been associated with higher rates of severe toxicity at therapeutic capecitabine dosing include increased age, pre-treatment with uracil, decreased renal function, decreased body surface area, female sex, and the use of capecitabine in combination therapy [24]. Abnormal hepatic function has not been clearly associated with increased risk of toxicity [33, 72, 75].

Data characterizing acute, one-time lethal doses of capecitabine and 5-FU in patients or subjects not undergoing treatment for malignancy is scarce. According to Burns and colleagues, Hoffmann-La Roche reported an LD50 in male Swiss mice of 365 mg/kg [96]. Johnson et al. reported a murine LD90 of 458 mg/kg [97]. A third study found that 50 mg/kg of 5-FU given once daily for 3 days resulted in 40% mortality in a mouse model while 60 mg/kg resulted in 100% [98]. Interestingly, the lethal dose is thought to vary based on circadian rhythms [96]. With respect to capecitabine specifically, the FDA reports that doses up to 2000 mg/kg are not lethal in mice, rats, or monkeys [11]. There is no data available regarding changes to bioavailability in the overdose setting for either medication.

Pathophysiology

The pathophysiology of toxic effects and the pharmacology of therapeutic effects are largely the same. Fluoropyrimidines are designed to kill cells; they preferentially destroy malignant cells, but in killing tumors, they may also damage normal tissue. There are, however, two unique toxicities that bear mentioning: hand-and-foot syndrome and fluoropyrimidine-induced cardiotoxicity.

Hand-and-foot syndrome, also known as palmar-plantar erythrodysesthesia and chemotherapy-induced acral erythema, is one of the few side effects seen more commonly in patients on capecitabine rather than 5-FU [11, 15, 99]. The mechanism is not entirely clear, but one popular theory suggests that higher concentrations of thymidylate phosphorylase in the palms as well as increased basal cell proliferation may be responsible [99–101]. Another study found a significant correlation between the presence of a particular methylene tetrahydrofolate reductase genotype and the development of hand-and-foot syndrome [30].

Reports describing the epidemiology of fluoropyrimidine-induced cardiotoxicity vary in their assessments. Most reports suggest a prevalence of around 4% [102–107]. In a review of 1350 patients without pre-existing cardiac disease, however, only 1.2% of patients were found to have cardiac complications [108]. Symptoms can range from asymptomatic EKG changes to myocardial infarction (MI), heart failure, and cardiogenic shock [104, 109]. Patients may also develop cardiomyopathy with left ventricular systolic dysfunction, ventricular dysrhythmia, arterial vasospasm, and direct endothelial damage. The pathogeneses of these phenomena are not entirely known [103, 108, 110–112]. Coronary vasospasm has historically been considered the most significant contributor to cardiotoxicity [108]. More recently, researchers have suggested that endothelial dysfunction, thrombus formation, direct myocardial damage, and accumulation of cytotoxic 5-FU metabolites may also play a role [108, 111]. The majority of case reports and review articles describing 5-FU- and capecitabine-induced toxicity describe symptoms occurring while patients are actively undergoing therapy [104, 105, 108–111, 113, 114]. Its occurrence appears to be dependent on the dose and means of administration; its relationship to pre-existing cardiovascular disease is unclear [102, 103, 107, 114].

Clinical Presentation

Toxicity from fluoropyrimidines may be considered as being on the spectrum of adverse effects due to chemotherapy. The Common Toxicity Score (CTS) developed by the National Cancer Institute (NCI) characterizes all symptoms of toxicity from mild adverse effects to death according to a five-point scale. Grade 0 describes absent symptoms, grade 1 mild, grade 2 moderate, grade 3 severe and undesirable, grade 4 life-threatening or disabling, and grade 5 death. The definition of mild, moderate, severe, etc. depends on the particular toxicity in question (e.g., neurologic versus hematologic) [115]. To the emergency physician, symptoms consistent with grades 3, 4, and 5 are the most concerning.

Common adverse effects from 5-FU and capecitabine include fatigue, nausea, vomiting, stomatitis, abdominal pain, hyperbilirubinemia, anemia, leukopenia, and neutropenia (neutropenia being the most common hematologic toxicity) [11, 26]. Peripheral sensory neuropathies may also occur, as well as nonspecific neurologic findings including headache, dizziness, and insomnia. Alopecia, venous thrombosis, and predisposition to infection are among other complications. The frequency of each adverse event and the proportion of patients who develop severe or life-threatening signs and symptoms depend on patient characteristics, the type of malignancy being treated, and the treatment protocol being used. (5-FU demonstrates different rates of adverse events when it is delivered as a bolus versus as a continuous infusion; rates also vary when fluoropyrimidines are administered as monotherapy versus combination therapy.) As discussed, capecitabine is generally better tolerated than

5-FU although it is associated with higher rates of hand-and-foot syndrome. Cassidy et al. reported stomatitis in 61.6% of patients with metastatic colon cancer on 5-FU with leucovorin while 24.3% developed stomatitis on capecitabine. In the same study, 10.3% of patients developed neutropenia on 5-FU versus 1.2% of those on capecitabine [1, 10–12, 14–16, 24, 26, 35, 72, 116].

Death and life-threatening toxicity are generally associated with neutropenia, leukopenia, severe diarrhea, and mucositis. A combination of these effects, especially neutropenic fever and mucositis or diarrhea, can lead to sepsis, shock, and multi-organ dysfunction [19, 24, 26, 80]. Death from therapy occurs in about 0.4–2% of patients, and severe toxicity frequently presents during the first treatment cycle [16, 24, 26, 27, 80]. Other rare but potentially fatal complications include central neurologic dysfunction and 5-FU-induced cardiotoxicity. Neurotoxicity may vary in presentation: ranging from confusion and altered mentation to frank encephalopathy and coma [80, 117–121].

The clinical manifestations of cardiovascular toxicity are described in the section on toxicokinetics. They range from asymptomatic EKG changes to cardiovascular collapse. The more dramatic presentations, including myocardial infarction, coronary dissection, ventricular dysrhythmias, cardiogenic shock, and heart failure, are likely to be obvious to the emergency physician. Death from cardiotoxicity results most frequently from heart failure and sudden cardiac death. Patients can also present, however, with anginal symptoms, asymptomatic ST segment changes, and QT interval prolongation [103, 106, 108, 112, 114, 122–124]. Rezkalla et al., in a prospective study, found that 68% of patients receiving 5-FU infusion had asymptomatic ST segment changes (versus 24% who had asymptomatic abnormalities prior to treatment). The study reported that while CK-MB concentrations generally increased during treatment, ST segments all returned to baseline by the end of the study and no patients developed myocardial infarction. Of note, however, two of the patients who developed ST segment changes and ventricular ectopy during therapy died within hours of completing the study; new infarctions were not noted on patient autopsies [109]. In another study, De Forni et al. found that 62.5% of patients who developed anginal symptoms during treatment demonstrated myocardial dysfunction on echocardiogram (ECHO). All ECHOs returned to normal within 2–6 days [123].

Hand-and-foot syndrome, a characteristic adverse effect of fluoropyrimidines, is generally graded according to a three-point severity score [11]. Symptoms range from paresthesias or painless swelling of the palms and soles (grade 1), to painful erythema and edema which do not interfere greatly with activities of daily living (grade 2), to obvious desquamation, blistering, ulceration, and pain which interfere with daily activities (grade 3) [11, 100, 101].

Evaluation and Diagnostic Testing

A diagnosis of fluoropyrimidine-induced toxicity is made by history, physical exam, and laboratory assessment. Laboratory tests may include a complete blood cell count and complete metabolic panel, including liver enzymes. If a patient complains of anginal symptoms, an EKG and troponin should be obtained, and an echocardiogram should be considered. Given the frequency with which patients develop silent ischemia (including ST segment changes without chest pain), physicians may consider performing an EKG on even those patients who do not present with anginal symptoms. If an EKG is performed and is found to be abnormal, consideration should be given to performing cardiac enzymes [109]. Other testing should be directed toward the patient's chief complaint (e.g., blood cultures for infection, lumbar puncture in the setting of acute altered mentation, etc.). There are no specialized laboratory tests that are required emergently, and there is no need to obtain plasma 5-FU concentrations. This test will not change management and it may take days to weeks to result.

Management

Management of patients presenting with fluoropyrimidine-induced toxicity consists first and foremost of stabilization, resuscitation, and supportive care. Consultation with the treating oncologist, if possible, is recommended. In many cases, toxicity can be managed with simple dose reduction [10, 11, 15, 30, 72, 88, 100, 113]. Uridine triacetate is the well-publicized and expensive antidote for fluoropyrimidine-induced toxicity. Its indications are limited, however, and ideally an emergency physician would discuss giving this medication with an oncologist and/or toxicologist prior to its administration. Uridine triacetate will be discussed in the section that follows.

With respect to cardiotoxicity specifically, stabilization and supportive care take priority. Given that most patients who develop cardiotoxicity are actively undergoing treatment with a fluoropyrimidine, one of the first steps consists of discontinuing therapy (i.e., turn off the infusion pump). Prophylaxis and treatment with calcium channel blockers and nitroglycerin have been studied, with incon-

sistent results [103, 106, 112, 125]. Given the conflicting data, it seems appropriate to consider these medications in consultation with a cardiologist, oncologist, or toxicologist, and, more importantly, to use conventional therapies (e.g., follow standard ACLS guidelines) in patients who are unstable [106, 108, 112]. There is insufficient evidence to recommend the use of steroids in the setting of cardiotoxicity [110]. Patients with anginal symptoms and elevated cardiac enzymes should be admitted to the hospital, their cardiac enzymes trended and consideration be given to performing an ECHO [108, 123]. The treating oncologist or cardiologist should be consulted regarding the management of patients undergoing therapy who present with asymptomatic EKG changes and without laboratory evidence of ischemia.

Neurotoxicity appears to respond to aggressive supportive care and to withholding chemotherapy [118–121]. Uridine triacetate should be considered if the patient otherwise meets established criteria.

Treatment for hand-and-foot syndrome is similarly supportive (pain control and wound care as needed). Immersing hands and feet in cold water and applying topical emollients may be beneficial [101]. It is also generally recommended that treatment be discontinued, or the dose be reduced, until symptoms resolve [11, 15, 100]. Dose adjustments should be made in consultation with the treating oncologist. Steroids are not recommended due to insufficient evidence of benefit [100].

Toxicity related to 5-FU's interaction with CYP2C9 should be managed supportively, and any long-term dose adjustments to medications such as warfarin or phenytoin should be made in consultation with the treating oncologist and/or the patient's prescribing physician [10, 77, 78, 126].

Granulocyte colony-stimulating factor (G-CSF) may be considered to treat myelosuppression, even in addition to uridine triacetate [26, 79, 90, 127, 128]. Recommendations on the administration of G-CSF are available from an article by Smith et al. on behalf of the American Society of Clinical Oncologic [128]. The decision to administer G-CSF should be made in conjunction with the treating oncologist.

Extracorporeal elimination has not been studied in the setting of overdose or early-onset severe toxicity. The FDA suggests that dialysis may reduce the plasma concentration of cytotoxic 5-FU metabolites [11]. Given these compounds' large volumes of distribution and rapid elimination in urine, and the lack of data to support this intervention, renal replacement therapy for fluoropyrimidines is only recommended for those patients who already require the therapy (e.g., end-stage renal disease, profound acidemia, etc.) [37, 69, 129].

Antidotal Therapy: Uridine Triacetate

Uridine triacetate (UTA) is the acetylated oral prodrug of uridine, a pyrimidine analogue consisting of uracil bound to a ribose ring. Once absorbed in the gut, it is deacetylated to form uridine. Uridine is subsequently converted to uridine triphosphate (UTP) which competes with FUTP for incorporation into RNA [80, 81, 126]. It has a time to peak serum concentration of 2–3 hours and is absorbed into cells via nonspecific nucleoside transporters [126]. It is metabolized via typical pyrimidine catabolic pathways and also excreted renally [126]. Uridine triacetate is dosed in adults as 10 grams every 6 hours for a total of 20 doses. In pediatric patients it is dosed at 6.2 grams/m^2/dose, up to 10 grams, for a total of 20 doses [126]. It is typically well tolerated; adverse effects include vomiting, nausea, and diarrhea [80, 126].

According to the FDA, uridine triacetate is indicated in two settings. The first is after overdose of 5-FU or capecitabine, defined on the package insert as "the administration of fluorouracil at a dose, or infusion rate, greater than the intended dose or maximum tolerated dose for the patient's intended regimen of fluorouracil." Uridine triacetate is indicated in this setting regardless of the presence of symptoms. No distinction is made between intentional, unintentional, and iatrogenic overdoses. Its second indication is in the setting of "early-onset, severe or life-threatening toxicities affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity and/or neutropenia)" that occur within 96 hours of the patient completing a 5-FU infusion or capecitabine administration [126].

The evidence for the use of uridine triacetate in humans comes largely from studies by Ison et al. in 2016 and Ma et al. in 2017, which compared the outcomes of patients in two open-label, single-arm trials to historical case controls. The studies demonstrate a difference in survival at 30 days of 96% in those who received uridine triacetate (97% in those with overdose and 86% in those with early-onset symptoms) versus 16% in those who did not. Of those patients who developed early-onset symptoms but started uridine triacetate over 96 hours after last dose administration, only 38% survived. All deaths among patients with early-onset symptoms occurred in this cohort. Of note, this study included both pediatric and adult patients, and several patients received UTA via nasogastric, orogastric, and gastrostomy tubes [80, 81]. Since these studies were published, multiple other authors have reported success in reversing toxicity with uridine triacetate [79, 130–132].

Ma et al. defined severe or life-threatening signs and symptoms as "severe cytotoxic mucosal and/or hematologic toxicities as well as acute encephalopathy and/or cardiomy-

opathy" [80]. The FDA's indications for uridine triacetate are broader. If possible, it is recommended to consult with the treating oncologist when deciding to administer UTA as this medication not only may undermine 5-FU's therapeutic effects but is expensive and potentially difficult to obtain [133, 134]. In situations where the degree of toxicity is unclear, or where it is unclear if toxicity requires therapy, it is recommended to consult with an oncologist and/or a toxicologist.

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Part V

Palliative Care

Emergency Department Use at End of Life

55

Hsien Seow and Kayla McMillan

Introduction

As cancer treatments advance and patients with cancer are living longer, there is also a growing potential for increased visits to the emergency department (ED) at end of life. End-of-life (EOL) care specifically refers to the final weeks of a patient's life, when symptoms commonly increase in intensity and death approaches [1]. EOL care is related to palliative care, which is a holistic approach to care, with emphasis on preventing or relieving suffering and improving quality of life [2]. Stakeholders have been advocating for improved EOL care and earlier integration of palliative care into the cancer trajectory for over two decades (Fig. 55.1) [3]. The American Society of Clinical Oncologic endorsed a clinical practice guideline supporting the provision of early palliative care concurrently with standard oncologic care in 2017 [4]. Without effective EOL or palliative care, many dying cancer patients have unmet clinical needs, uncontrolled symptoms, and poor quality of life, as well as fear, anxiety, and depression, which may cause them to visit the ED [5]. Avoiding unnecessary ED visits may lead to economic benefits (ED visits and the ensuing hospital care are costly), improve patient experience (many patients do not want to be cared for in a hospital or ED at the EOL), and improve quality of care (some causes of ED visits are avoidable with proper planning).

The ED is a setting of care focused on the management of acutely presenting medical problems. It is a fast-paced work environment with an emphasis on identifying the problem and instituting a solution over a very short interval of time. In contrast, dying cancer patients typically have complex medical histories, multiple symptoms, and difficult psychosocial circumstances. Therefore, optimal EOL care requires a great deal of time to honestly discuss prognostic information, make clear recommendations, facilitate patient-family discussions, affirm patient choices, address holistic/psychosocial aspects of well-being, and plan for unexpected changes in a patient's condition. This is the antithesis of care typically provided in the ED. EOL trajectories in the ED have been characterized as being either "spectacular" (e.g., sudden, traumatic death) or "subtacular" (e.g., slow process of dying or a nonemergency death) [6]. ED staff are well trained to deal with "spectacular" deaths but often distance themselves from patients dying "subtacular" deaths. As a result, EOL

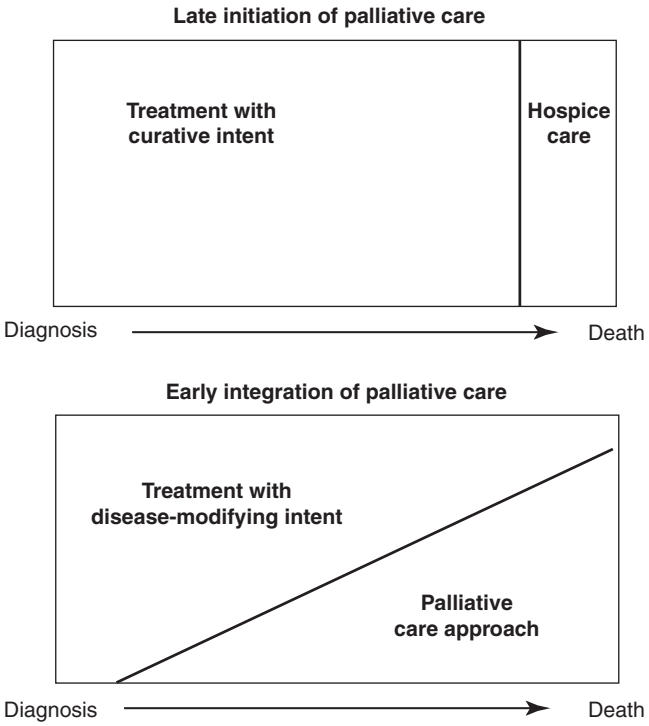

Fig. 55.1 Models comparing late initiation and early integration of palliative care for cancer [3]

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care in ED is typically far from ideal. Hence, ED visits at the EOL are a widely used indicator of poor-quality care [7, 8].

There have been a few literature reviews on EOL care in the ED that were not cancer-specific. One review focused on the evidence for managing dying patients in the ED and identifying areas for improvement [9]. The authors observed that of the 160 papers included in the overview, the 6 main themes that arose were (1) the uncertainty of treatment in ED for patients at EOL; (2) quality of life issues; (3) costs; (4) ethical and social issues; (5) interaction between ED and other services; and (6) strategies for out-of-hospital care. Another similar review focused on barriers to providing optimal care in the ED. Of the 27 studies included, they identified minimal resources, lack of staff education, and outdated models of care as the main challenges [10]. A third review focused on older adults at EOL in the ED and identified 14 articles [11]. The review noted there was limited evidence regarding the definition, clinical profile, care delivery, and outcomes for older people requiring EOL care in the ED, though they did note that there were multiple tools available for dealing with EOL care, including predicting mortality and assessing functional status, comorbidities, symptom distress, palliative care needs, quality of life, and caregiver's stress. Nonetheless, the growing numbers of older adults, the increased pressures of access to high-quality care in a timely manner, and the escalating costs of healthcare delivery are bringing more attention to appropriate use of ED services, especially for cancer patients at the EOL with well-documented symptom needs.

This chapter will review the topic of ED use at the EOL with a specific focus on cancer patients. It will review:

1. The rationale for investigating ED use at EOL
2. The frequency with which ED visits occur
3. Common reasons for ED visits at the EOL
4. Factors associated with ED visits at the EOL
5. Evidence for strategies to mitigate ED use at the EOL

Case Study

Mr. X, a 75-year-old white male, presents to the ED at 11:00 pm with increasing abdominal pain and worsening fatigue over the past several days. He is accompanied with his wife, who is his primary caregiver at home. Mr. X has been a patient of your hospital for many years, and as such you look up his records in the hospital EMR. From the EMR you learn that Mr. X was diagnosed with squamous cell carcinoma of the lung approximately 7 years ago and underwent a wedge resection 5 years ago. Since his lung resection, he has also had chemotherapy. He and his wife live in a suburb outside of town, which is where his primary care doctor is located. Also from the EMR, you learn that approximately 5 months ago, Mr. X. was diagnosed with a metastasis in his brain. He has been followed by his oncologist in the outpatient setting. You can also see that he has not met with the palliative care service which is available at your hospital.

After you have read about his history in the EMR report, you decide to ask Mr. X and his wife some questions to gain his understanding about his illness and his current symptoms. After discussing his abdominal pain, you rule out any other contributing factors, and provide symptom management for him, as well as you provide a prescription to last him until he is scheduled to see his family doctor in the community next.

After assessing for any other contributing factors, it is likely that his fatigue is related to his decline in overall functioning. After speaking with him and his wife, you understand that he is unable to get out of bed most days, and he is having trouble walking without assistance. You ask Mr. X about his outpatient follow-up, in order to ascertain whether he has been seen by a palliative care specialist in the community. His wife lets you know that he has not; no one has suggested this to them. You take a few minutes to explain why a palliative care service is appropriate for him, and after letting him discuss it with his wife, they agree to be referred to the service at your hospital so they can see someone quickly. You refer him to your inhospital palliative care team, and request an urgent consult, given his advanced illness and his steady decline. Once the palliative care team member arrives, you give handover to ensure seamless transition and that no details are missed, including letting them know you gave him a prescription for pain medicine.

Rationale for Investigating ED Use at EOL

Indicator of Poor-Quality Care

In 2003, Earle et al. published a landmark paper describing quality indicators of EOL cancer care that could be measured with administrative healthcare data [7]. The impact of this publication was significant because (1) stakeholders began to discuss the merits of the quality indicators, selected through literature review, focus groups with patients and family members, and an expert panel, and (2) researchers began measuring them using readily available administrative healthcare data. One of the key indicators of poor-quality care identified was frequent ED visits near the EOL. It became operationalized as more than one ED visit in the last 30 days of life [8]. The rationale for this indicator is because high rates of unplanned medical encounters at EOL, exemplified by ED visits, may indicate overuse of aggressive care, inattention to symptom issues, poor planning by providers to anticipate patient needs, insufficient support or education for the caregivers, lack of advance directives, or inadequate availability of palliative care resources, such as hospice ser-

vices; when these elements are provided or addressed, they can help avoid unnecessary ED visits at EOL. Examples of other poor-quality care measures that emerged from this publication include a short interval of time between chemotherapy and death, ICU admissions near EOL, and a short time interval between hospice enrollment and death.

Patients and Families' Perspective on ED Visits at EOL

Cancer patients will frequently visit the ED when symptoms are uncontrolled and they find themselves with unmet needs [12]. Many would prefer care by their usual provider or someone from the cancer center where they typically receive care. However, when the need arises and patients present at their local ED, it presents a challenge to the emergency physician [13].

Most reports indicate that patients prefer to be at home at the EOL [14–17]. Earle et al.'s original indicator [7] was developed by including perspectives from 12 patients with incurable cancer and 4 family members: they associated ED visits primarily with toxicity management of aggressive chemotherapy. Early in the trajectory, this was expected and described as a necessary part of receiving therapy. Later in the trajectory of care, patients' willingness to tolerate toxicity for non-curative therapy diminished. In turn, their willingness to endure ED visits or accept them as a necessary component of care also diminished. Interestingly, in a study of Japanese bereaved family members, only 14% endorsed the appropriateness of frequency of ED visits as an indicator of poor-quality care. This suggests that this particular measure may be perceived differently in different cultures where the perspective on a "good death" may be different [18].

In a study of stakeholder perspective of quality indicators for EOL care, 16 women with metastatic breast cancer and 8 bereaved family caregivers participated in focus groups to provide their perspectives on quality indicators at EOL [19]. The dominant themes that emerged were support for, access to, and early enrollment for palliative care services, continuity of care, and multidisciplinary care. The authors do not describe a dominant theme related to ED visits, though ED visits clearly disrupt continuity of care in the ambulatory setting and lack of adequate access to palliative care may lead to ED visits.

Healthcare Provider Perspective on ED Visits at EOL

Healthcare providers strongly endorsed ED visits as a quality indicator. In a Delphi process conducted in Canada with healthcare professionals evaluating the acceptability of frequency of ED visits near the EOL, more than 80% of participants agreed the indicator was meaningful and important [19]. An American qualitative study of perspectives of care providers in the ED, including physicians, nurses, and other providers, revealed several emerging themes. These include conflict among providers about the feasibility and desirability of providing palliative care in the ED, not seeing a difference between palliative care and EOL care, poor communication between providers in the inpatient and outpatient setting, conflicts about withholding life-prolonging treatment, and inadequate training in pain management. A similar study from Germany describes ED physicians as having difficulty dealing with palliative patients because of uncertainty regarding aspects of psychosocial care and EOL decision-making [20]. Relatedly, a survey from Australia indicates that ED physicians feel that the care they provide to EOL cancer patients is futile [21]. These sentiments conceptually endorse the notion that, from a provider perspective, the ED may not be the best place to care for this patient population.

System Perspective on ED Visits at the EOL

In some jurisdictions, ED use at EOL is being measured at a population level and has even become a system-wide metric in some countries. In Australia, routine data from the Department of Veterans Affairs showed that cancer decedents averaged one ED visit in the last 6 months of life [22]. Another study in Australia examined the ED use in the last year of life among cancer and non-cancer patients revealing that 70% had at least one ED visit [23].

In the UK, the National EOL Care Intelligence Network, now a part of Public Health England, is measuring ED use for quality improvement. In 2018, a study by Henson et al. discovered that as many as 30.7% of patients in the UK who died of any cancer had at least one ED visit [24]. In another UK study for urological cancer patients in the last year of life, they found that emergency admissions tended to be significantly longer and more costly than planned admissions to hospital. As well, emergency admissions were far more common than planned admissions to hospital in the three largest urological cancer groups [25].

In the USA, the Veterans Health Affairs Department has reported data on ED visits at end of life [26]. At a national level, the American Society for Clinical Oncologic has included the "percentage of patients who died from cancer with more than one emergency department visit in the last 30 days of life" as a measure for voluntary reporting for their end-of-life module in the Quality Oncologic Practice Initiatives (QOPI) [27]. For instance, one cancer center reported their ED visit admission rate as 68% in their last month of life, compared to peer healthcare institutions

reporting an average of 32% [28]. Nonetheless, the difficulty of risk stratification to separate those for whom the ED visit was appropriate versus avoidable continues to be a challenge for its use as a national quality indicator for accreditation [29].

In Canada, the cancer agency for Ontario has created the "Cancer System Quality Index" which for many years included ED visits in the last 14 days of life as a quality indicator (www.csqi.on.ca). The index, published annually on the Internet, includes a plethora of quality indicators for cancer across the care trajectory. For instance, in their 2016 report, they noted that 40% of cancer patients visited the ED in the last 2 weeks of life [30]. Nationally, the Canadian Partnership Against Cancer has begun measuring this quality indicator in their annual system performance reports. For instance, in their 2017 report, they noted that 49% of cancer patients who died in hospital visited the ED once, 25% twice or more, and 27% no times in their final 28 days of life [31].

Frequency of ED Visits at EOL

The frequency of ED visits depends on several definitional and contextual factors. Table 55.1 [7, 23, 31–51] lists a review of publications describing the frequency of ED visits at the EOL. These publications typically used population-based retrospective cohort studies linking large administrative data. They were conducted in Canada, the USA, Australia, Egypt, England, Mexico, and Taiwan, ranging in cohort sizes from 154 to 272,832, where years of study periods spanned 1991–2018. The prevalence of ED visits ranged from 1.5% having two or more ED visits in the last 30 days of life [32] to 85% having an ED visit in the last 6 months of life [33]. The duration of the observation window from death varies from 2 weeks to 1 year, with 30 days being most common. The patients in the numerator may be counted with any ED visits, but in several papers, more than one visit is required. Many studies are population based, but some are institutional. Some include all cancer types, where others include only specific cancers. These differences in study design, definitions, and inclusion/exclusion criteria should be considered when making comparisons.

The majority of studies used an observation window looking backwards from the date of death to create a decedent cohort (i.e., people who have died) rather than a prospective cohort that followed patients until they all died. This approach has been criticized since people who have died may not be the same people one would identify as actively dying [53]. However, when used with administrative data, this approach allows for easy identification of relevant cohorts, efficient study of all patients who died (rather than a nonrandom subset), and timely evaluations for quality improvement [54].

Contextual factors must also be considered. Specifically, what are the palliative care supports available for study participants, and more generally, how is care structured? For example, in Warren et al., ED use was compared in Ontario, Canada, and the National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) regions in the USA. The methods of the study explicitly harmonized all definitions in both jurisdictions to ensure a fair comparison. ED rates differed by about 10%, which is likely a reflection of differences in health policies, structures, and process of care in the two settings, such as access to home care, medications, and hospice services [43].

Despite these differences, most authors conclude that ED use in cancer patients at EOL is too high and that this population-based metric should be driven down as low as possible. Studies examining regional variation have attempted to define a benchmark rate. Earle et al. in 2005 described the regional variation in ED visit rates at the EOL among Medicare beneficiaries with cancer; they found almost threefold variation among 11 different regions in the USA [55]. They defined an empiric benchmark as the top decile of performers to derive a benchmark of <4% with more than one ED visit in the last 30 days. This benchmark was achieved in only one other study in a community setting [56]. In fact, the majority of the studies with a similar definition exceed this proposed benchmark. For instance, Barbera et al. examined 33 health regions in 3 provinces in Canada, and the top decile had a 34% ED visit rate [57]. While negative publication bias may partially explain this, the existing data support the impression that improvements in care are required. It is important to remember that this measure is meant to be considered at a population level. It would be impossible to have a system where the value of this measure is zero. ED care may be entirely appropriate for a particular individual. But when population values are in excess of 30%, one ought to further examine the health policies and systems of care. This was reinforced by a Canadian study of cancer decedents by Seow et al. which showed ED visit rates at EOL varied more greatly by provinces than by community population size [58].

Reasons for ED Visits at the EOL

There have been several studies examining why cancer patients go to the ED, though most do not restrict their evaluation to the EOL period. Mayer et al. conducted a study identifying over four million ED visits in North Carolina, USA [59]. The top three complaints were related to pain, respiratory distress, and gastrointestinal issues. Beyond treatment, in a Korean study of over 5500 cancer-specific ED visits, 55% of visits were related in some way to disease progression [60]. This disease progression often leads to worsening

Table 55.1 Frequency of ED visits at end of life

First author	Year of publication	Country	Jurisdiction	Cancer type	Cohort size	Time window prior to death	Patients to ED (%)
Allende-Pérez et al. [34]	2020	Mexico	Mexico City	Any cancer	426	30 d	8.9% >= 3 ED admissions
Henson et al. [24]	2018	England	England	Any cancer	124,030	30 d	30.7% 1 visit; 5.1% >=1 visit
Falchook et al. [32]	2017	USA	Five geographic regions	Lung, CRC, breast, GI, prostate	28,731	30 d	1.5–2.5% for >=2 ED visits
Seow et al. [33]	2016	Canada	Ontario	Any cancer	54,576	6 mo	85%
Alsirafy et al. [35]	2016	Egypt	Single institution	Terminal cancer	154	3 mo	77%
Obermeyer et al. [36]	2016	USA	SEER Medicare	Any cancers	272,832	6 mo	81%
Lee et al. [37]	2015	Taiwan	Taiwan	Any cancer	23,883	1 yr	81.5%
McNamara et al. [38]	2013	Australia	Western Australia	Any cancer	746	12 mo/90 d	65%/47%
Miesfeldt et al. [39]	2012	USA	SEER Medicare	Poor prognosis cancer	235,821	30 d	10% with >= 1 ED
Maddison et al. [40]	2012	Canada	Nova Scotia	CRC	1201	30 d	23.2%
Ho et al. [41]	2011	Canada	Ontario	All cancer deaths	227,161	30 d	8.6–10.5% with >= 1 ED visit
Saito et al. [42]	2011	USA	SEER Medicare	NSCLC	7879	30 d	23.2% with >= 1 ED visit
Warren et al. [43]	2011	USA/ Canada	SEER Medicare/ Ontario	NSCLC	13,533 US/8100 ON	30 d	37% US/49% ON
Rosenwax et al. [23]	2011	Australia	Western Australia	Cancer or nine other conditions	1071	12 mo	70%
Bergman et al. [44]	2011	USA	SEER Medicare	Prostate cancer	13,804	6 mo	mean # visits: 1.53
Barbera et al. [45]	2010	Canada	Ontario	Ovary, endometrium, cervix	2040	2 wk	34%
Keating et al. [46]	2010	USA	VA matched with SEER	Lung or CRC	2913 in each group	30 d	13.1% >=1 ED [VA]; 14.7% [SEER]
Setoguchi et al. [47]	2010	USA	Pennsylvania	Lung, breast, CRC, prostate	7565	30 d	38.90%
Barbera et al. [48]	2010	Canada	Ontario	Any cancer	91,561	6 mo/2 wk	83.8%/33.9% >=1 ED visit
Tang et al. [49].	2009	Taiwan	Taiwan	Any cancer	242,530	30 d	16–21%
Smith et al. [50]	2009	USA	SEER Medicare	Lung, CRC, breast, prostate	40,960	30 d	5–10% with >= 2 ED
Barbera et al. [51]	2008	Canada	Ontario	Lung cancer	5855	2 wk	32.20%
Earle et al. [8]	2004	USA	SEER Medicare	Lung, breast, CRC, other GI	28,777	30 d	7.2–9.2% with >=1 ED visit
Burge et al. [52]	2003	Canada	Nova Scotia	Any cancer	8702	After dx	mean # visits: 1.33

CRC colorectal cancer, *GI* gastrointestinal, *SEsER* Surveillance, Epidemiology, and End Results Program, *NSCLC* non-small cell lung cancer, *VA* US Department of Veterans Affairs

symptoms. Indeed, one study showed that physical symptom burden in the ambulatory cancer setting was strongly associated with the likelihood of an ED visit [61].

A systematic review of reasons for ED use by all cancer patients revealed that many visits are likely chemotherapy-related toxicity as demonstrated by frequent visits for fever, neutropenia, and gastrointestinal complaints [62]. Another review also identified fever, urinary complaints, malnutrition, neutropenia, and gastrointestinal complaints as main reasons [63]. Similarly, a third study examined 18 EDs in the USA and found that three-quarters of cancer patients presenting to ED had undergone cancer treatment in the past 30 days and over 60% had advanced or metastatic cancer [64]. The five most common ED diagnoses were abdominal pain, fever, shortness of breath, nausea/vomiting, and throat/chest pain [64].

A few studies focused on cancer ED visits at end of life. In one Canadian study of over 91,000 cancer patients, they identified 36,600 ED visits in the last 2 weeks of life. The main reasons for visits to ED in the last 2 weeks are listed in

Table 55.2 Top ten reasons for ED visits in the last 2 weeks of life [48]

Rank	Reasons	Frequency	
		(no.)	(%)
1	Lung cancer	3242	8.9
2	Dyspnea	1844	5.0
3	Pneumonia	1832	5.0
4	Abdominal pain	1126	3.1
5	Malaise and fatigue	1084	3.0
6	Palliative care	1042	2.9
7	Dehydration	944	2.6
8	Pleural effusion	717	2.0
9	Altered consciousness	689	1.9
10	Pancreatic cancer	585	1.6

Table 55.2 [48]. Pain was responsible for about 5% of visits. As well, dyspnea, pneumonia, and pleural effusion were also very common. This study used administrative sources of data and was limited by the coding system for the diagnoses associated with each visit. As such, lung cancer was the most common "reason," although this does not actually reveal the cause of the visit. This likely reflects the impact of progression of disease in a common cancer type and is consistent with other works specific to lung cancer [51]. In a US study of cancer patients who died in the ED in the state of North Carolina, over one-third of those deaths had a cause of death due to lung cancer. Across all cancer deaths, the most common chief complaints were respiratory, gastrointestinal, and neurological [65]. Similarly, a Turkish study examining ED visits within a month of death identified dyspnea as the main complaint, with lung cancer as the most common cancer [66]. In the Netherlands, a study of advanced cancer patients visiting the ED within 3 months of death found that pain and dyspnea were the main reported symptoms [67]. A nationwide population-based study of Taiwanese cancer patients at end of life also identified "symptoms, signs, and ill defined conditions" as the main cause of admission for a third of cases, using ICD-9-CM diagnosis codes [37]. A study in Singapore looking at reasons for ED visits among cancer patients in the last week of life identified breathlessness as the cause for nearly 60% of patients, followed by pain (35%), general weakness or lethargy (27%), and decreased appetite (24%) [68].

Pain management warrants specific attention because it is commonly experienced by ambulatory cancer patients at the EOL [1] and often leads cancer patients to visit the ED [48, 59–62]. Two studies, one with Canadian patients and another from the USA, indicate that about a third of cancer patients have inadequately managed pain [69, 70]. In a study from Mexico, uncontrolled pain was also one of the principal reasons for ED visits [34]. This observation is essentially unchanged over the past two decades [71]. Meanwhile, emergency physicians have indicated they are not comfortable managing pain in this population [50]. Furthermore, overcrowding, a common ED problem, is associated with worse pain management [72]. Cancer patients deserve meticulous management of their pain by those best trained to do so.

When considering why patients visit the ED, a natural follow-up question is whether the visit was possibly avoidable or was the ED the best and only place for the patient to receive care? In a Canadian study, potentially avoidable visits were defined as ED visits related to a technical issue, such as catheter issues or prescription refills, and occurred about 1% of the time in the last 2 weeks of life. 8.4% of visits were for reasons such as malaise, fatigue, or need for palliative care, which likely represent some version of the patient "not coping" at home [48]. Arguably, these visits are also avoidable. In one small Irish study that prospectively documented reasons for ED visits in cancer patients who were under the care of a specialist palliative care program, about half of the visits were felt to be avoidable [73]. To a certain extent, the concept of avoidable ED visits is highly dependent on the alternative places available for care delivery. In the absence of readily available access to care elsewhere, ED visits may not be avoidable at all.

In summary, cancer patients at the EOL visit the ED because of symptoms related to their malignancy. Pain and respiratory issues are common, as are difficulties coping at home. Chemotherapy toxicity is a problem for all patients, regardless of their trajectory, and contributes significantly to ED visits.

Factors Associated with Increased Risk of ED Visits

ED visits at EOL have been shown to be associated with several different patient, tumor, treatment, and health system factors. However, the differences in definitions and populations studied lead to inconsistent results in the literature.

Among patient factors, sex has been most consistently demonstrated as an important factor with men more likely to visit the ED than women [8, 39, 41, 49, 52, 74–77]. Age is also important with older patients less likely to make visits [8, 39–41, 45, 49, 52, 75, 77–79]. Those with more significant comorbidity are also more likely to visit the ED [8, 41, 63, 74, 75, 80]. This is due to the complications related to chronic comorbidities, such as an exacerbation of COPD symptoms [81]. With one exception [40], those living in rural regions are also more likely to visit the ED [41, 52, 74–76, 78, 82]. ED visits are also more likely for patients who live in lower-income neighborhoods [52, 74, 76], with some exceptions [75]. Race has also been shown to play a factor [63].

Some tumor and treatment factors have been examined. Hematologic patients are more likely to make ED visits than

patients with solid tumors [41, 79]. Among solid tumors, those with lung cancer are at the highest risk [74, 76, 77]. Patients with higher symptom burden are more likely to visit the ED [61]. Treatment factors are also important. Patients with metastatic cancer receiving chemotherapy are more likely to visit the ED [83]. As will be reviewed in the next section, palliative care interventions may decrease the likelihood of ED visits.

The influence of healthcare system factors has also been demonstrated. For example, as previously mentioned, harmonized comparisons between countries give some insight into the possible effects of different systems, such as the US hospice system versus more generalized access to palliative care [43]. Similarly, within the USA, those within the Department of Veterans Affairs (VA) system were less likely to have ED visits than those enrolled in Medicare [46].

Evidence for Strategies to Mitigate ED Use at EOL

It is unrealistic to expect that all ED visits at the EOL can be avoided. An ED visit can be a very taxing ordeal for patients at this point in their cancer journey, and most agree it happens more often than is desirable. This section will review the evidence for interventions that mitigate and reduce visits to the ED for patients at the EOL. A number of different studies have found that having access to palliative care programs can reduce ED visits for patients with advanced cancer at the end of life. For example, Temel et al.'s study in a comprehensive cancer care, where patients with advanced non-small cell lung cancer were randomized to early palliative care versus usual care, showed that early referral could reduce ED visits. Those randomized to the intervention arm experienced fewer ED visits in the last 30 days of life (22% versus 30%) [84]. Evidence also exists for community-based palliative care interventions to reduce ED visits. A randomized controlled trial of home-based palliative care versus usual care also demonstrated a decrease in ED visits for those in the intervention arm, from 33% to 20% [85]. In addition, a pooled matched analysis of a retrospective cohort that was exposed to a specialized palliative home care team or usual home care demonstrated that the risk of having an ED visit at the EOL was 32% less for those who received care from the specialized palliative care teams [86]. The impact of early palliative care referral has also been demonstrated in observational datasets. For example, an Australian cohort of 28,331 decedents residing in an area with community-based palliative care program found that those who had the program initiated (58% of cohort) had less unplanned ED visits in the last 6 months of life [87].

Another study that showed access to palliative care services reduced ED visits was conducted as part of the Cancer Care Outcomes Research and Surveillance Consortium. This was a prospective cohort study of 1231 patients with stage IV lung or colorectal cancer, which demonstrated that patients who had an EOL discussion more than 30 days prior to their death were much less likely to use acute care services (ED and hospitalization) in the last 30 days [88]. A single-institution retrospective chart review of 220 women who died of ovarian cancer found that when an EOL discussion occurred more than 30 days prior to death, visits to the ED decreased [89].

Palliative care programs work because they can address many different factors of serious illnesses. Some of these include improved symptom control, decreased chemotherapy use, and improved knowledge of expectations. This was shown by Temel et al. in that patients in an intervention arm had better quality of life as well as less depression and anxiety [84]. Temel's study also revealed longer survival for those receiving palliative care. Palliative care is often provided by specialized care teams that are interdisciplinary, providing more opportunity for education and symptom management. They also tend to provide home-based services and are available 24/7. Nonetheless, some of the challenges to integrating palliative care into oncologic ED are the delays in palliative care consultations, patient and family expectations, and the fast-paced ED culture with limited resources [81].

While palliative care programs are important to reduce and avoid unnecessary ED visits, what can be done for those patients who do visit the ED? One intervention used a brief negotiated interview which allowed ED clinicians to motivate patients to have their needs met [90]. Another option for managing palliative care patients in the ED is to implement a screener questionnaire to identify patient needs, including cancer patients. In one study, a screener was integrated in the hospital's electronic health record system, which ultimately triggered referrals to consultants based on the results of the questions, e.g., pharmacy consult for medication reconciliation or social work consult for unmet needs at home [91]. This study showed that novel pathways and integrated communication led to many of the patients having their needs met quickly and efficiently. Another example of an intervention used in the ED is the Choosing Wisely campaign, which urged ED physicians to proactively engage with palliative care and hospice care services. One study used the Choosing Wisely campaign to create a pathway from ED to more appropriate services [92]. The ED physicians in the study would contact the palliative care team directly during regular office hours and allow them to decide next steps or, if during weekends or evenings, patients would be referred to a "hot clinic." The "hot clinic" saw patients in a timely manner, usually within a week of the ED visit. Another study in South Korea developed a dedicated ED cancer unit to specifically manage oncologic emergencies [60].

However, not all palliative care intervention studies in the ED have been positive [93–95]. Some studies have been positive for other outcomes, such as satisfaction, cost, or hospitalization, but not for ED visits [93, 96, 97]. For example, Bakitas et al. published a palliative care randomized trial using a nursing-led, multicomponent, psychoeducational intervention in a comprehensive cancer center [93]. This trial showed improvements to quality of life and mood, but did not reduce ED visits at the end of life. In a systematic review of the literature, DiMartino et al. could not substantiate whether palliative care interventions were more effective than usual care at reducing ED visits [98]. The nature of interventions and the different ways of reporting outcomes are perhaps a few reasons for the differing results.

It is important to recognize some of the factors that may explain varying outcomes in studies of ED visit mitigation. Intensity of care is important to note as a possible factor. In a study of patients receiving palliative home nursing, Seow et al. demonstrated a dose response such that patients receiving more nursing hours of care at home were less likely to visit the ED [75]. Studies conducted in two different provinces in Canada have demonstrated that increased continuity of physician care in the outpatient setting also decreased ED visits [52, 76]. Another factor may be a patient's access to hospice services. In one study, patients using hospice services were compared to matched cases who did not [36]. Patients enrolled in hospice services had less ED visits than their matched controls.

Structural aspects, for example, of a palliative care team, the health system, or the care setting itself, are also important. A case series of four regions with either high or low ED visit rates demonstrated that regions with lower ED rates have specific features of their palliative care systems that were absent in the other regions [99]. These included overall palliative care needs planning, a common chart, standardized patient assessments, 24/7 palliative care team access, advance practice nursing expertise available, and designated roles for the provision of palliative care services. Related to the physical structure of care settings, some jurisdictions have restructured the ED to create cancer-specific ED programs as an alternative place for assessment [60]. This particular structural change would facilitate easier access with short waits for cancer patients. It would also potentially hone the expertise of the ED staff working there and improve communication with the ambulatory team. Such an approach, however, seems to result from failure to optimize care upstream in the trajectory.

Future Directions

The literature provides some opportunities for better providing EOL care in the ED, when these unavoidable visits happen. These include providing education to ED clinicians on the holistic nature of end-of-life care and educating staff on enhancing their communication techniques [10]. There is also opportunity for future research in this area. There has been little to no research evaluating the impact of psychoeducational interventions for informal caregivers on ED visits at EOL. A systematic review of informal caregivers' needs identified a lack of practical support for nursing skills [100]. The clinical approach taken for patients at EOL may be quite different [101] and may require additional training and skills. A systematic review of qualitative and quantitative studies of unmet needs for patients and carers identified that the most frequently unmet need was effective communication with healthcare professionals [102]. Another future opportunity is further exploration of hospital integration of palliative care divisions within EDs, which could lead to better coordination with existing services such as social workers, psychologists, or caseworkers [81].

Conclusion

Most practitioners are familiar with the aphorism, "To cure sometimes, to relieve often, to comfort always." The field of medicine has excelled in technical aspects of providing care, and we cure much more often than we did in the past. As a result, the importance of offering relief and comfort is sometimes forgotten. Population-based measures of ED visits in cancer patients at the EOL are a meaningful indicator of quality of care. With administrative healthcare data, this measure is easy to follow. Currently, ED visits are happening more often than is desirable. Increased efforts are needed to minimize the use of toxic therapies at the EOL and to create effective palliative care structures and processes which are readily accessible.

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Pain Management

56

Danielle M. McCarthy and Laurie M. Aluce

Case Study

A 56-year-old man with a history of metastatic pancreatic cancer receiving gemcitabine chemotherapy presents to the ED with 2 days of worsening abdominal pain. He describes the pain as sharp, constant, located throughout his entire abdomen, and ranks it an 8/10 on the numerical pain rating scale. He also feels nauseated and has not had a bowel movement in 2 days. He denies fever or urinary symptoms.

He states that his cancer-related chronic pain is usually well controlled with his fentanyl patch and extended release morphine, so he usually only needs a couple doses of his PRN immediate-release morphine per day. In the last 24 hours, however, he has taken the immediate-release morphine exactly every 4 hours due to pain.

The nurse asks the physician, "What would you like to give for pain?" The physician is torn. The etiology of the pain remains unclear, and he does not want to make any potential opioid-induced constipation worse. The patient is in a severe pain crisis, however, so the physician decides to treat with IV opioids while awaiting imaging results. He orders 6 mg IV morphine.

After 15 minutes, the patient remains in severe, 8/10 pain despite the morphine. He is not exhibiting any adverse side effects from the opioids. The physician wonders if he should order a higher dose of morphine. After consulting his equianalgesic table and converting the patient's home pain medication requirements into IV morphine equivalents, the physician realizes he severely under-dosed the first round of morphine. The physician orders a second, more appropriate dose of IV morphine, which provides adequate relief to the patient.

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Introduction

Pain is one of the most common symptoms experienced by patients with cancer. Prevalence estimates (pooling patients with multiple types of cancer and in various stages of treatment) suggest that >50% of cancer patients experience pain [1]. The prevalence of pain is higher for patients who have metastatic or advanced stage disease, and greater than a third of cancer patients rate their pain as moderate or severe [1]. The prevalence of pain in the subset of cancer patients visiting the emergency department is less well defined. It is estimated that approximately 10–41% of all ED visits made by cancer patients involve pain as the primary complaint [2, 3]. Regardless of the chief complaint that prompted the ED visit (e.g., presenting primarily for pain crisis or presenting for infectious symptoms), giving analgesics is among the most frequent treatments provided to cancer patients in the ED. The severity of patient self-reported symptoms, including pain, is a reliable predictor of emergency department visits [4, 5].

Classification of Pain

The National Comprehensive Cancer Network states that a "pain crisis" is an occasion on which a patient is experiencing severe pain (at least a numerical rating of 8 on a 10-point scale) [6]. Such a pain crisis may arise from inadequate control of a patient's baseline persistent pain or may be a more acute pain crisis superimposed on a well-established history of chronic pain. Such pain is commonly referred to as "breakthrough pain." While breakthrough pain may result from cancer progression, it may also result from increased analgesic tolerance or end-of-dose failure. Similar to the more general pain prevalence estimates detailed above, nearly two-thirds of patients with chronic cancer pain syndromes experience breakthrough pain episodes [7]. In general, it is accepted that a patient's baseline persistent pain must be well

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controlled before attributing the pain episode to "breakthrough pain" [8].

Such pain crises require a rapid response from emergency physicians to achieve adequate analgesia. The approach to a pain crisis should be similar to the emergency physician's approach to any other emergency and include an assessment of the history, severity, timing, and location of the pain, in addition to a thorough physical exam. In addition to classifying pain in cancer patients as baseline pain or breakthrough pain, other important considerations when assessing pain in cancer patients include the following: awareness of the pain mechanism or pathophysiology, consideration of the triggers of the pain crisis, and discussion of the goals of care.

Pain Severity

Many tools are available to assess pain severity and thereby quantify pain. Examples of such pain severity assessment tools include numerical rating scales (NRS), visual analogue scales (VAS), and picture scales (e.g., Faces Pain Scale). More in-depth assessments, which often incorporate numerical or visual analogue rating scales, are also available and include the Brief Pain Inventory, the McGill Pain Questionnaire, and the Memorial Pain Assessment Card. Pain is subjective, and at times in the ED, high pain scores are greeted with skepticism; therefore, it is important to use one of these validated measures to assess patients' pain. This is particularly important for patients with chronic pain who may not exhibit more objective signs (e.g., grimacing) or vital sign changes such as tachycardia [9]. Using a pain score measure, and applying it consistently, will help to add a more objective means of reproducibly tracking patients' pain and response to treatment over time. Although any of the abovementioned measures are validated and can be useful if applied consistently, for purposes of ED evaluation of cancer pain, a numerical rating scale (NRS) is preferred [10, 11]. Specifically, in cancer patients, a NRS has better capability to distinguish between a patient's background or chronic pain and breakthrough pain [11]. The NRS is an 11-point scale ranging from 0 to 10. When asking patients to rate their pain on this scale, it is important to provide consistent verbal anchors to the scale [12]. Most commonly, the anchors are "0 = no pain" and "10 = worst pain possible" or "10 = pain as intense as you can imagine" [10].

In addition to pain ratings, it is important to ask patients their expectations regarding pain relief. Asking "At what level of pain do you feel comfortable?" recognizes that patients with chronic pain, including those with chronic cancer pain, do not necessarily expect pain intensity scores to reach zero [13]. Use of such personalized pain goals may allow adequate analgesia while avoiding the overtreatment of pain and resultant adverse effects.

Pain Mechanisms

In addition to assessing pain intensity, the pathophysiology and trigger of the pain should be considered. No universally accepted system for classifying cancer pain exists [14]. Nonetheless, cancer pain is often described in terms of the pathophysiology of the pain and is broadly divided into nociceptive or neuropathic pain. Nociceptive pain is caused by tissue injury and can be further subdivided into visceral pain (from organs) or somatic pain (related to bones, joints, soft tissue). Visceral pain (e.g., peritoneal carcinomatosis) is more poorly localized than somatic pain (e.g., bone metastases). Neuropathic pain is related to dysfunction of nerves; this dysfunction may be central or peripheral and has many possible etiologies, including direct compression of a nerve or related to treatment (e.g., inflammation post-radiation). Often, those with cancer suffer from complex pain states combining both nociceptive and neuropathic mechanisms. Chronic pain in cancer survivors may have a unique etiology and symptomatology [6]. Studies have shown that chronic pain affects approximately one-third of cancer survivors and that, even among survivors who are disease free, approximately one-third continue to use opioids long term [15, 16]. Considering the pathophysiology of the pain is important because different types of pain may respond to treatments differently. Additionally, patients with cancer may suffer from non-cancer-related pain syndromes such as pre-existing diabetic neuropathy or arthritis pain. Although these pain syndromes are not directly related to the cancer, they can nonetheless contribute to patients' psychological distress and suffering.

Other historical factors, such as recent treatments and the stage of the cancer, can also aid the emergency physician in defining a trigger for the pain. This information can help the physician determine if the pain represents a reversible pain crisis, an anticipated worsening related to recent treatment, or a worsening related to progression of disease. A new pain or pain in a new location may represent disease progression and as such may require more extensive diagnostic evaluation than an increase in intensity of a known chronic pain.

Before beginning an extensive diagnostic search for the cause of a new pain and before starting a patient on a new analgesic, it is important to discuss the goals of care with the patient as part of a shared decision approach to care. These conversations can be difficult because of the lack of a pre-existing relationship, but are nonetheless important. The extent of the patient's diagnostic evaluation will depend on their goals of care and should take into consideration the risk or discomfort of diagnostic tests and what action would be taken with different results of those tests.

Oligoanalgesia

Any discussion of pain control in emergency medicine should include a discussion of oligoanalgesia – the underuse of analgesics. Oligoanalgesia has been a problem for cancer patients but is perhaps improving in recent years. A recent review found that the percentage of cancer patients with undertreated pain decreased from 43% to 32% over the course of 6 years [17]. This estimate implies that, while there has been an improvement in the treatment of pain in cancer patients, many patients seeking care in the ED for breakthrough pain may still have had inadequate baseline pain control. In fact, one recent study found that opioid-tolerant cancer patients were less likely to receive an adequate initial pain medication dose in the ED if they had higher home opioid doses [18]. Psychosocial factors such as depression, spiritual concerns, or misconceptions regarding prescribed medications may also contribute to oligoanalgesia in cancer patients [19]. The problem of oligoanalgesia for these patients is then compounded by a well-established history of oligoanalgesia in the ED itself. Specifically, recent studies have found that pain is undertreated in the ED and that disparities in pain treatment exist related to age and race [20–23]. Many factors likely contribute to oligoanalgesia in the ED. One concern in particular relates to significant tension between providing adequate analgesia and ongoing concerns relating to drug misuse, addiction, and deaths from prescription opioids in the USA [24]. According to the Centers for Disease Control and Prevention, the overall opioid prescribing rate decreased 19.2% between 2006 and 2017, with the largest annual reductions occurring in the most recent 4 years [25]. A study regarding opioid prescribing practices between 2007 and 2013 showed that opioid prescribing stayed relatively constant for cancer patients while it increased by approximately 2% for non-cancer patients [26]. Further research will need to be conducted to monitor these trends and watch for possible decreases in opioid prescriptions to cancer patients as the opioid epidemic continues and overall opioid prescribing declines. In the context of the cancer patient in the ED, the immediate focus should be on controlling the breakthrough pain during the ED visit. Decisions about new prescription analgesics from the ED can be made in conjunction with the treating oncologist or palliative care physician.

Treatment Options

Treatment of cancer pain should be individualized. There are many treatment modalities available to the cancer patient, including pharmacologic, interventional (e.g., injection therapies, neural blockade), rehabilitative (e.g., therapy for lymphedema), psychological (e.g., cognitive behavioral therapy), neurostimulation, or integrative (e.g., massage) [27, 28]. Those modalities may be applied singularly or in a combined modality fashion. Most of these therapies are not immediately accessible to the emergency physician; thus, while an awareness of these therapies is important, the primary tools at the emergency physician's disposal to improve pain are pharmacologic.

WHO Analgesic Ladder

Over 30 years ago, in 1986, the World Health Organization published recommendations for the management of cancer pain. These recommendations included a three-step analgesic "ladder" intended to guide the selection and escalation of analgesics [29] (Fig. 56.1). This model has been frequently used for not only cancer pain but other painful syndromes. Over the intervening 30 years, modifications to the existing ladder have been suggested, including eliminating the second step of the ladder, adding a fourth step, or "fast tracking" patients to the top of the ladder [30, 31]. When considering the individual patient, it is important to reconcile evidence-based clinical guidelines and new information (e.g., new medications, importance of risk assessment) with the original WHO consensus-based guidelines [27]. However, the WHO analgesic ladder provides a good framework for the

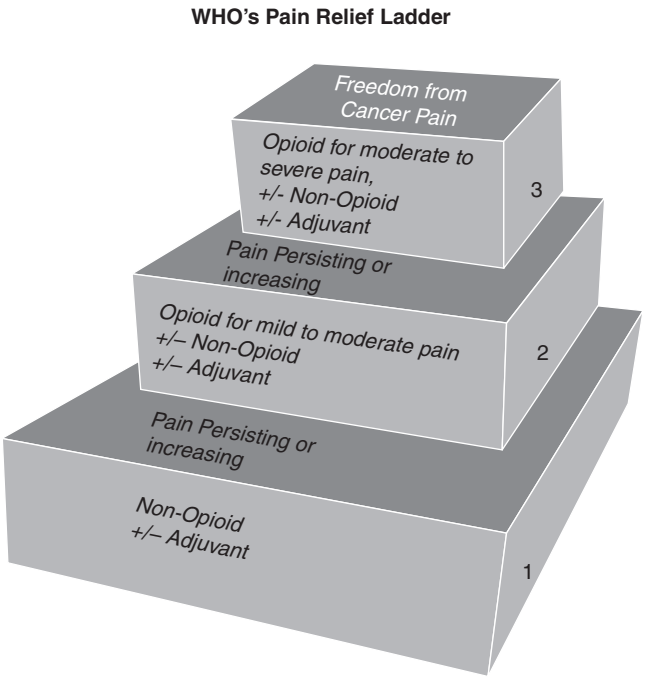

Fig. 56.1 WHO analgesic ladder. (Reprinted with permission of The World Health Organization: http://www.who.int/cancer/palliative/pain-ladder/en/. Accessed 18 Mar 2020)

discussion of the different types of analgesics and the rationale that analgesic choice should be given commensurate to the patients' pain intensity, as measured by a pain scale.

Non-opioid Analgesics

Non-opioid analgesics include nonsteroidal anti-inflammatory medications (NSAIDs) and acetaminophen. These medications are useful in the management of acute and chronic pain. One limitation of both NSAIDs and acetaminophen is a "ceiling effect" wherein increasing the dose above a certain level does not provide any additional pain relief. The ceiling effect therefore limits the ability of these medications to be titrated for severe pain; however, even when NSAIDs and acetaminophen alone are insufficient for pain control, they should be considered as a co-analgesic to opioid treatment because they may reduce the dose of opioid needed to achieve pain control.

Acetaminophen is a non-salicylate analgesic that does not have any antiplatelet activity. It does not have clinically detectable anti-inflammatory effects; however, it may be a useful analgesic for some conditions. One concern with acetaminophen is potential hepatotoxicity. The FDA advises that doses in patients with normal liver function should not exceed 4000 mg/day, and the National Comprehensive Cancer Network (NCCN) panel suggests that providers consider limiting chronic administration of acetaminophen to 3000 mg or less per day [6].

NSAID medications possess both anti-inflammatory and analgesic properties. These medications act by inhibiting isoforms of an enzyme called cyclooxygenase (COX); inhibition of this enzyme results in decreased synthesis of prostaglandins. Different classes of NSAIDs have varying selectivity for the isoforms of the COX enzyme (COX-1 and COX-2). Depending on the source of the patient's pain and comorbidities, a choice of a nonselective or selective NSAID can be made. Patients who respond to one of the NSAIDs may not respond as well to others. NSAID medications also have significant side effects that should be considered prior to administration. All NSAIDs cause a reversible decreased platelet aggregation (while the drug is at therapeutic serum concentrations). If patients already have a high risk of bleeding, the use of NSAIDs should be carefully considered. All NSAIDs can cause gastrointestinal (GI) adverse effects, ranging from dyspepsia to bleeding gastric ulcers. Medications to protect the gastric mucosa, such as a proton pump inhibitor (PPI), should be considered to minimize the risk. NSAIDs can also lead to renal insufficiency through multiple mechanisms, and caution should be used when patients have risk factors for renal impairment, including advanced age, dehydration, diuretic use or multiple myeloma.

Opioid Analgesics

When a patient's pain is not adequately controlled by non-opioid analgesics, opioid analgesics represent the next step on the WHO analgesic ladder. Opioid medications can be classified as naturally occurring opioids (e.g., morphine, codeine) and semisynthetic (e.g., dihydromorphone, oxycodone) or synthetic compounds (e.g., fentanyl, methadone). Opioids can further be classified by their action at the opioid receptor (agonist, partial agonist, or antagonist) and by the receptor where they primarily function (mu, delta, or kappa). Opioid receptors exist in both the central nervous system and the peripheral tissues; however, the clinical effects of opioids are thought to be related primarily to the opioid action on central rather than peripheral receptors [32].

Tramadol is a mixed-mechanism drug that acts as a weak mu opioid receptor agonist but also demonstrates some norepinephrine and serotonin reuptake inhibition. A recent Cochrane review concluded that there is little evidence to support the use of tramadol for cancer pain and that it is less effective than morphine [33].

Opioids can be administered by multiple means, including oral, transmucosal, rectal, transdermal, intranasal, subcutaneous, or intravenous routes. The intramuscular route is generally not recommended as it provides no pharmacologic advantage over subcutaneous administration and has the disadvantage of causing additional pain. If time permits, the oral route of administration is preferred [29]; however, for patients in a severe pain crisis, more rapid pain control may necessitate the use of intravenous opioids. Opioids, with the exception of methadone, follow first-order kinetics and achieve their peak plasma concentration (and maximal analgesic effect) along a similar timeline: 60–90 min for oral/rectal administration, 30 min for subcutaneous/intramuscular administration, and 6–10 min for intravenous administration [19, 34].

If time permits the administration of an oral opioid, it is also important to remember that many oral opioids are combination pills with a non-opioid analgesic (e.g., acetaminophen). The presence of the non-opioid limits titration of the medication orally to avoid toxicity from the co-analgesic (e.g., maximum of 4000 mg/day of acetaminophen).

For those patients in more severe pain, or requiring intravenous dosing for other reasons (difficulty swallowing), there are many available intravenous opioids. For the opioid-naïve patient, morphine is a safe, standard drug to start therapy [6, 35]. However, morphine should be used with caution in patients with renal impairment because one of the active metabolites (morphine-6-glucoronide) can accumulate with renal dysfunction. For intravenous dosing of the opioid-naïve patient, a starting dose of 2–5 mg of morphine (or equivalent) is recommended. This dose should be followed by a reassessment at 15 min, and if the pain score remains

Table 56.1 Equianalgesic dosing[a]

Opioid	Oral dose	Parenteral dose	Duration of action (h)
Morphine	30 mg	10 mg	3–4
Hydrocodone	30 mg	–	4–8
Hydromorphone	7.5 mg	1.5 mg	3–4
Oxycodone	15–20 mg	–	3–6
Fentanyl[b]	–	50–100 μg	1–2

[a]This table is a guide only. Equianalgesic dosing tables vary subtly and this table should not replace more in-depth review of dosing
[b]Applies to IV conversion only. For transdermal fentanyl conversion, see package insert

unchanged or increased, the initial dose given should be increased by 50–100%. If the pain score is decreased but still moderate (e.g., 4–7), the same initial dose should be repeated, and if the pain level is low (e.g., 0–3), then the initial dose can be used as needed [6].

For the opioid-tolerant patient (a patient that takes at least 60 mg/day oral morphine, 25 mcg/hr transdermal fentanyl, 30 mg/day oral oxycodone, 8 mg/day oral hydromorphone, 25 mg/day oral oxymorphone, or an equianalgesic dose of another opioid for 1 week or longer), the drug choice will likely be informed by their home medications and prior opioid use [6]. Patients may be on a combination of opioid medications at home (e.g., transdermal and oral preparations or long-acting and immediate-release preparations). In order to identify the approximate opioid use of a patient at home, and thereby to more accurately estimate their pain control needs in the ED, equianalgesic dosing tables can be used (Table 56.1).

Equianalgesic dosing tables were first constructed in the 1960s and 1970s to codify the relative potency of different opioid formulations. These tables can be used to calculate patients' baseline outpatient opioid use. Recently, experts have expressed concerns over the limitations of the data used to construct the dosing tables and their applicability in the clinical realm [36, 37]. Specifically, the studies used to construct these tables were primarily acute rather than chronic pain. Research also suggests that there is significant variability in the dose needed to achieve pain relief between individuals which may be influenced not only by prior exposure to opioids but also by age, gender, and genetic polymorphisms that affect opioid binding [9]. Given this potential for wide variability in dose response, the equianalgesic dosing recommendations as well as the starting doses noted above should be considered a guideline, to be individualized by the practicing physician.

When using the equianalgesic dosing tables, the first step is to calculate the patient's "equianalgesic dose equivalent" based on the analgesic use over the previous 24 h. After choosing the opioid to administer, the initial IV dose will be determined by converting the previous 24-h requirement to a total IV equivalent. Once a 24-h IV equivalent has been calculated, the first dose should be 10–20% of that total dose [6]. After the first dose is given, a reassessment should occur within 15 min, and, similar to opioid-naïve patients, if the pain level remains ≥8, the dose should be escalated by 50–100%. If the pain is moderate (e.g., 4–7), the same initial dose should be repeated, and if the pain level is low (e.g., 0–3), then the initial dose can be used as needed [6].

Another reason to exercise caution when switching opioids is because of opioid cross-tolerance. Patients on opioids will develop tolerance; this is expected. One of the signs of tolerance is achieving less pain relief from the same dose of the medication. One approach to optimize pain control when tolerance is present is to switch (or rotate) the opioid being used. In other clinical situations, opioid rotation may be useful to minimize adverse effects. Although there is some cross-tolerance between opioids, it is not complete. This incomplete cross-tolerance is due to many factors, including individual variations in metabolism, concurrent medications that impact metabolisms, and individual variations in opioid receptors. Due to this variability in individual response when switching opioids, it is recommended to first calculate the equianalgesic dose and then to decrease the calculated dose by 25–50% [9, 36]. Ultimately, the clinical situation should be considered when choosing a 25% reduction vs. a 50% reduction, including factors such as the patient's pain control and individual adverse effect profile. Two medications with exceptions to the 25–50% automatic reduction are methadone and fentanyl. Methadone has a nonlinear relationship to other opioids [19]. When switching to methadone, larger automatic dose reductions are recommended (75–90%) [27]. Converting to transdermal fentanyl should follow the calculated equianalgesic dose in the package insert and does not require an automatic dose reduction [28]. Initiation and titration of methadone and fentanyl are complex and should only be done by emergency physicians in consultation with the treating oncologist, pain specialist, or palliative care team.

Opioid Side Effects

Opioid analgesics have many potential side effects that may make patients or prescribers reluctant to use the medications or use them in adequate doses to achieve pain control. Patients can develop a tolerance to certain side effects (e.g., nausea or respiratory depression); however, other side effects (e.g., constipation) are not decreased with chronic use (Table 56.2). Several symptoms including pruritus and rash may result from either allergy or direct opioid effects from mast cell degeneration and histamine release. True anaphylaxis to opioids is rare, but can occur. Care must also be taken to distinguish between opioid side effects and the underlying clinical manifestations of comorbidities such as dehydration or drug interactions [38].

Table 56.2 Adverse effects of opioids

Adverse effect	Develop tolerance	Treatment
Constipation	No	Use laxative prophylactically
Pruritus	No	Opioid rotation
Nausea	Often	Opioid rotation Anti-nausea medications
Sedation	Yes	Decrease or rotate opioid Discontinue other medications that can cause sedation
Respiratory depression	Yes	Decrease or rotate opioid Discontinue other medications that can cause sedation Sedation will precede respiratory depression
Delirium	No	Decrease or rotate opioid Discontinue other medications that can cause delirium Avoid sedating medications unless necessary and consider the use of antipsychotic medications
Hyperalgesia	No	Rotate opioid Use non-opioid medication/strategy

Respiratory depression is one of the most feared side effects of opioids; however, tolerance can develop in a period of days to weeks of being on opioids, and it is rare in patients taking opioids chronically. Respiratory depression occurs in a dose-dependent fashion due to opioid action at the brain stem respiratory centers. Concomitant use with other sedating medications, such as benzodiazepines, may increase the risk for respiratory depression. Sedation precedes respiratory depression. If there is a concern for respiratory depression (from either home medications or medications administered in the ED), naloxone can be administered. Naloxone is an opioid receptor antagonist which will reverse the effects of the opioid; however, the half-life of naloxone is shorter than the half-lives of many opioids, so patients need continued observation if there was a concern for respiratory depression. Naloxone can precipitate acute and severe withdrawal symptoms in the patient taking chronic opioids and should be administered cautiously. Diluting 1 mL of the standard 0.4 mg/mL concentration of naloxone in 9 mL of normal saline (for a total of 10 mL) and administering 1–2 mL (0.04–0.08 mg) approximately every minute until respiratory rate improves will allow reversal of respiratory depression while minimizing withdrawal symptoms.

Nausea is one of the most common side effects of opioids with estimates ranging from 10% to 40% of patients experiencing nausea [39]. Opioid causes nausea through several mechanisms including stimulation of the chemoreceptor trigger zone, slowed gastric emptying, and effects on the vestibular system. Depending on the source of the nausea, different antiemetics will have variable efficacy. Dopamine receptor antagonists (e.g., prochlorperazine or haloperidol) or serotonin antagonists (e.g., ondansetron) will be the most useful for nausea related to the chemoreceptor trigger zone, whereas promotility agents (e.g., metoclopramide) may have more impact when gastric stasis is causing the nausea.

Constipation is another common side effect that emergency physicians should anticipate in patients for whom they prescribe opioids. Among cancer patients on chronic opioids, the prevalence of constipation is as high as 90% [40]. Opioids slow bowel transit time and peristalsis, and tolerance to constipation does not develop over time. When a cancer patient presents with symptoms of constipation, it is important to rule out bowel obstruction/impaction before starting medications to treat constipation.

Pharmacologic agents to ease constipation are typically divided into five categories: bulk-forming agents, softeners, stimulants, osmotic agents, and peripheral mu opioid receptor antagonists. Bulk-forming agents increase fecal mass to stimulate peristalsis. Stimulants act by increasing intestinal motility, whereas osmotic agents (e.g., polyethylene glycol, lactulose) act by increasing water content in the large bowel. The NCCN recommends prophylaxis with both a stimulant (or pro-kinetic) agent and the osmotic agent polyethylene glycol [6]. Bulk-forming agents and stool softeners are unlikely to be effective in isolation. A 2010 Cochrane review recommended the use of polyethylene glycol over lactulose for chronic constipation because of better outcomes related to stool frequency, form, associated abdominal pain, and use of additional products [41]. If constipation persists despite the above medications, the provider can titrate the existing regimen or add an additional agent, such as magnesium hydroxide [6]. Two peripherally acting mu opioid receptor antagonists may be considered if laxative therapy has failed. Both methylnaltrexone, administered subcutaneously or orally, and naloxegol, an orally active agent, have demonstrated efficacy in reversing opioid-induced constipation [42, 43].

Adjuvants (Co-analgesics)

Adjuvant medications, also known as co-analgesics, are a diverse group of drugs that may have a primary indication other than pain; however, they work to enhance the effects of traditional analgesics, "have independent analgesic activity in certain painful conditions, or counteract the adverse effects of analgesics" [9, 44]. The emergency physician may not be starting these medications in the ED to achieve pain relief in the acute setting; however, it is important to have a familiarity with these medications both when taking the patient's history and when discussing future treatment options with their outpatient oncologist or palliative care team.

Adjuvant medications are on every step of the WHO pain ladder, and they encompass many drug classes, including

Table 56.3 Adjuvant drugs for use during ED cancer pain crisis[a]

Category	Example	Indication	Comments
Corticosteroids	Dexamethasone Methylprednisolone	Spinal cord compression Bone metastases Neuropathic pain	Often used to treat emergencies associated with cancer progression (e.g., spinal cord compression) but also have utility for other painful conditions including bone metastases and neuropathic pain The use of corticosteroids should be discussed with the oncologist given possibility of affecting treatment course
Benzodiazepines	Lorazepam Diazepam	Anxiety Muscle spasm	Use with opioids can be limited because of sedation
Anticonvulsants	Gabapentin Pregabalin	Neuropathic pain	Dose adjustment for renal insufficiency is required. Initiation requires close follow-up for titration
Anesthetics			
Local	Topical lidocaine 5% patch	Neuropathic pain	FDA approved to be worn for 12 h and then removed for 12 h
Systemic	Ketamine	Intractable pain	Dissociative anesthetic without significant respiratory depression Use of low-dose (sub-anesthetic) ketamine + opioids for treatment of acute cancer pain is an area of ongoing research
Intraoral	Magic/miracle mouthwash Lidocaine gel	Mucositis	Used in conjunction with parenteral opioids and good oral care regimens

[a]Other adjuvant drugs include antidepressants, stimulants, bisphosphonates, and cannabinoids; these drugs are not included in the table because they are less likely to be used in the acute pain setting in the ED

antidepressants, corticosteroids, anticonvulsants, local anesthetics, muscle relaxants, and benzodiazepines. The addition of some of these medications may result in a better balance of patient safety and efficacy of pain relief. However, caution must be used to avoid oversedation or other side effects related to polypharmacy as many co-analgesics are potentially sedating.

Specific adjuvant medications that may be useful to emergency physicians for use in patients with pain crises are outlined in Table 56.3.

Psychosocial Support

There are many non-pharmacologic interventions that have been shown to be helpful for cancer pain, including physical interventions (e.g., massage, physical therapy), cognitive-behavioral interventions (e.g., breathing exercises, music), and spiritual interventions (e.g., chaplain support) [6]. While emergency physicians likely won't have access to all of these modalities when treating acute pain, it is important for them to provide psychosocial support and perform a focused assessment of the patient's support system, cognitive status, and level of psychological or spiritual stress as this will likely affect therapeutic outcomes [19, 45].

Opioid Safety

As referenced earlier, providers may feel tension when attempting to balance the use of opioids to achieve adequate analgesia with the current public health crisis of addiction, misuse, abuse, overdose, and death related to opioids. Cancer patients are also at risk for these same adverse outcomes associated with opioids. Using validated screening tools, one ED-based study found that one-third of cancer patients on opioids presenting to the ED were at high risk for opioid misuse and suggest screening for opioid misuse in the ED [46]. In addition, the majority of cancer patients (and parents of pediatric cancer patients) do not store opioids safely, save unused opioids, and are unaware of how to safely dispose of opioids [47, 48]. Finally, a recent study found that the incidence of ED visits for opioid overdose in patients with cancer doubled between 2006 and 2015 [49]. Despite the fact that cancer patients are at risk for adverse outcomes associated with opioids, emergency providers must still strive to effectively control pain. The principles listed below can help emergency providers treat cancer patients with uncontrolled pain in the ED while also maximizing safe opioid use [6, 34, 50].

- Use as low of a dose as possible to achieve adequate analgesia and minimize side effects
- Avoid combining opioids with other potentially sedating medications, particularly benzodiazepines
- Titrate doses carefully, particularly in patients at high risk of adverse effects (patients with decreased renal/hepatic function, lung disease, upper airway compromise, sleep apnea, and/or poor functional status)
- Review prescription drug monitoring program databases if available and monitor patients for signs of misuse/abuse of opioids.
- Work closely with primary care doctors, oncologists, and palliative care teams, relay any concerns regarding misuse/abuse of opioids, discuss any new/updated prescriptions, and ensure close follow-up
- Educate patients and caregivers about safe use, storage, and disposal of opioids

EPEC-EM

The Education for Physicians on End-of-Life Care (EPEC™) curriculum is intended to teach the core competencies of palliative care and is a useful resource for physicians wanting to learn more about this topic [51]. Supported by the National Institutes of Health, the EPEC-Emergency Medicine curriculum is an adaptation of the original EPEC curriculum designed for those who work in the emergency department. One of the tenets of care advocated by EPEC™-EM curriculum and others is the rapid titration of opioids to achieve pain control.

Rapid Titration

Rapid titration of opioids has been advocated to achieve adequate pain control for patients presenting to the ED rather than traditional outpatient oral medication titration which can require several days to achieve analgesia [52]. Several different protocols, utilizing various opioids, have been evaluated in the literature and found to be safe [53–55]. The commonalities between the recommended protocols include having a formal numerical assessment of pain followed by administration of medications based on severity of pain and a formal reassessment of pain at a scheduled interval (ranging from 5 to 30 min). These cycle or reassessment and medication administration continue until either pain control is achieved or unwanted side effects limit further opioid use.

EPEC-EM advocates the following approach to the rapid assessment of cancer pain [19, 34]:

Step 1: Assess the patient and history This assessment should include discussion of the home medication use and dosing of both opioids and adjuvants. Additionally, the responsiveness of the pain to opioids should be estimated.

Step 2: Administer treatment For patients with severe pain (>7/10), IV medications should be given. For those with mild to moderate pain, the best route and choice of medication can be individualized based on the assessment and goals of care.

- For opioid-naïve patients: 0.1 mg/kg of IV morphine equivalent (less if patient is elderly or high risk).
- For opioid-tolerant patients: 10% of the previous 24-h IV morphine equivalents.

These recommend starting doses are guidelines and should be customized to the clinical scenario and take into account the patients' presentation, polypharmacy, and goals of care.

Step 3: Reassess the patient's pain, and reassess for unwanted side effects (somnolence or confusion) when Cmax has been achieved

The timing of the reassessment can vary based on when the maximum concentration (C_{max}) of the medication is reached (calculated by route of administration, e.g., approximately 15 min for IV administration). This timing is chosen because the maximum side effects will be experienced at the time of C_{max} [19]. Although parental agents will reach C_{max} faster than orally or subcutaneously dosed opioids, there is some variation within parental agents as to the speed of achieving peak plasma concentrations. Fentanyl, which is more lipophilic than morphine, can achieve peak plasma concentrations within 5 min and therefore may be particularly useful for rapid titration [52, 55].

Step 4: Achieve adequate pain control by redosing the medication if necessary For patients with persistent severe pain (>7/10) in whom no unwanted side effects have been noted, the initial opioid dose can be doubled. For those in whom there has been an improvement in pain control, but an unacceptable level of pain persists, the initial dose can be repeated. Both of these strategies will increase the effective C_{max} and thereby decrease pain.

Steps 3 and 4 should be repeated until pain control is achieved or side effects limit further administration of opioids. Additionally, adjuvant medications should be considered.

Step 5: Determine the plan for disposition, discharge instructions, and follow-up Patients whose pain cannot be adequately controlled in the ED should be considered for admission. Similarly, patients may have other medical conditions aside from pain that prompted their ED visit and should be admitted if further evaluation or treatment is needed. In the case that a patient presented solely for pain and the rapid titration of pain medication in the ED has controlled their pain, discharge can be considered. Adjustments to the patients' long-acting and breakthrough opioids can be determined based on patients' previous medication use, allergies, and tolerance of medications in the past. Methadone should not be started or titrated in the ED without consultation because of its complicated dosing. Communication with the patients' treating primary care physician, oncologist, or palliative care specialist is important, as is ensuring follow-up for the discharged patient.

Palliative Sedation

Distinct from the rapid titration of medications, another strategy that can be considered in the ED for pain control in cancer patients with intractable pain is "palliative sedation." A commonly accepted definition for palliative sedation ther-

apy is "the use of specific medications to relieve intolerable suffering from refractory symptoms by a reduction in patient consciousness" [56]. The goal of palliative sedation is to relieve distress and not to speed the dying process and therefore is distinct from euthanasia or physician-assisted suicide. Morphine has been used for the relief of dyspnea but is not effective at achieving sedation. Ketamine, a short-acting NMDA receptor antagonist, preserves respiration but can effectively achieve sedation and be used for intractable pain or agitation [57]. Emergency physicians will likely have some familiarity with ketamine from procedural sedations and use for acute, opioid-refractory pain, but when initiating it for palliative sedation, consultation with the palliative care team may be useful.

Consultation

Once the emergency physician has assessed the etiology of the cancer patient's pain, he or she may consider consulting specific services for assistance. Specific consulting services are outlined in Table 56.4.

Palliative Care in the Emergency Department

Consultation with the cancer patients' treating physicians, including their palliative care doctor, is useful not only in coordinating discharge but also in determining their treatment in the ED [58]. Some patients presenting to the ED may not have previously interacted with a palliative care physician; the emergency physician can and should consider consulting with palliative care if deemed necessary after an evaluation of the patient and discussion of wishes, regardless of patients' prior engagement with palliative care. The "Improving Palliative Care in Emergency Medicine" project has recommended the use of a screening tool to assist in the decision to consult palliative care from the ED [59]. If the patient has a serious, life-threatening illness (in the case of cancer, this includes patients with metastatic or locally advanced incurable disease) and any one of the following conditions, palliative care consultation should be considered:

- Not surprised: You would not be surprised if the patient died in the next 12 months.
- Bounce backs: The patient has had >1 ED visit or hospital admission for the same condition within several months.
- Uncontrolled symptoms: The current ED visit is prompted by difficult-to-control physical or psychological symptoms.
- Functional decline: Their presentation reveals a decline in function, feeding intolerance, unintentional weight loss, or caregiver distress.
- Increasingly complicated: There exist complex long-term care needs that require more support.

The ED is an important point of contact for patients with palliative care needs, and, more recently, there has been growing interest in studying the effects of palliative care in the ED [60]. A recent study found that greater than 50% of patients with active cancer presenting to the ED had at least one unmet palliative care need (e.g., uncontrolled pain, feeling overwhelmed, difficulty with getting care/medications) [61]. Despite this apparent need, few palliative care consults are placed from the ED; one study showed that only 5% of consults to palliative care occurred in the ED [62]. While the ED is a fast-paced environment and there are perceived barriers to consultation, research shows that screening and referral for palliative care consultation *are* feasible in the ED [63, 64]. One study even found that they were able to effectively screen for unmet palliative care needs in the ED and then offer services to address those needs using existing ED resources (e.g., pharmacist and social worker) without increasing ED length of stay [61]. A 2020 systematic review of the existing literature found that palliative care in the ED is feasible, may improve quality of life, and does not appear to decrease survival; the authors, however, were unable to determine its effects on healthcare utilization [60]. Further research is needed to determine the most efficient and effective method of linking palliative care with emergency medicine.

Table 56.4 Consulting services

Service	Indication
Oncologist	Discuss therapeutic plan, disposition
Palliative care	Symptom control, provide support
Pain specialists	Refractory symptoms, consideration for interventional strategies (e.g., nerve block, regional infusion)
Physical therapy, occupational therapy	Other modalities for pain control, improving pain related to movements
Psychiatry Social work Spiritual care	Relief of psychological pain Psychosocial support, relief of psychological pain Relief of suffering from unmet spiritual, existential needs

Summary

Patients with cancer often seek care in the emergency department, for both pain related to their condition and for other symptoms. Regardless of the symptom prompting the visit, it is important to assess and manage pain in this population. Multiple classes of medication to acutely control pain are

available to the emergency physician. It is important to assess the pain formally, using pain scales, and to discern if the pain crisis is related to progression of disease, expected breakthrough pain, or if a search for a new pain precipitant is needed. Regardless of the cause, pain should be managed quickly, and the patients' pain score should be frequently reassessed. The exact choice of medications will vary depending on the clinical situation and should be determined after reviewing the patients' home medications, comorbidities, and goals of care.

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Dyspnea in the Dying Patient

57

Ashley Shreves

Case Study

A 65-year-old female presents with severe shortness of breath. On review of the medical record, this patient has widely metastatic lung cancer, diagnosed 3 years prior, and recent imaging studies have shown progression of disease, despite chemotherapy and radiation. In the past 2 weeks, she has become weaker and has lost all interest in food. On review of the oncologic clinic notes, there has been discussion about enrolling the patient in a clinical trial, but her oncologist also suggested that she consider enrolling in hospice. In the ED, the patient's triage VS are abnormal: HR 120, RR 35, O2 sat 80%, BP 110/60, and temp 100. The patient is too ill to engage in discussions about goals of care, and her husband, who is her healthcare power of attorney, has not arrived to the hospital yet. The nurse asks: "Should we get everything ready for you to intubate the patient?" As there are no documented advance directives in the patient's electronic medical record and no surrogate decision-maker available for discussion, you decide to give patient a trial of noninvasive ventilation, while ordering labs and a chest X-ray, with the hopes of identifying the underlying etiology of her dyspnea. The patient initially tolerates the BIPAP well, with her RR improving from 35 to 25 and her oxygenation improving from 80 to 95%. She also appears more comfortable. Her labs show multiple abnormalities, including acute renal failure, an elevated troponin, a lactate of 5, and a WBC count of 20. Chest X-ray shows a small effusion and diffuse pulmonary metastatic disease, increased from the prior imaging study. When the patient's husband arrives, he tells you that his wife had actually decided to enroll in hospice but they hadn't had a chance yet and they panicked this morning when she became short of breath. He's certain that she would want to go home today, if hospice care could be arranged. You administer 2 mg morphine intravenously and this further improves her dyspnea. Thirty minutes later, she needs an additional dose: this time 4 mg is given. She is then weaned from the BIPAP and is comfortable on 4 L of oxygen, delivered via nasal cannula. Hospice is called and says they can manage the patient's dyspnea at home and can have all of the necessary equipment available, including oxygen, by the afternoon. Both the patient and her husband are comfortable with this plan, and the patient is discharged home with hospice care from the ED.

Introduction

Dyspnea is a broad, general term used to characterize any sensation of respiratory discomfort. In a statement by the American Thoracic Society from 2012, dyspnea was appropriately defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [1]. It is important to emphasize that dyspnea is indeed subjective and thus a *symptom*; this contrasts to classic *signs* of respiratory distress including tachypnea, nasal flaring, and accessory muscle activation. As such, a variety of language may be used to describe the sensation: terms such as breathlessness, shortness of breath, tightness, air hunger, difficulty breathing, labored breathing, and heavy breathing. All of these descriptors relate to an increased awareness of the breathing process—normally an unconscious physiologic activity—caused by any number of insults to be described later in this chapter.

As a common endpoint for multiple disease processes, dyspnea is remarkably prevalent in the advanced cancer population at the end of life. Some degree of dyspnea has been reported in up to one-third of all older adults living at home, approximately half of all patients admitted to tertiary care hospitals, 70–80% of patients with terminal cancer in the last 6 weeks of life, and up to 94% of patients with chronic lung disease at some point in the last year of life [2–6]. It is both debilitating for patients and emotionally upsetting for their families and caregivers. It also ranks among the most

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distressing symptoms at the end of life, leading to a marked reduction in the quality of life and a source of both fear and anxiety for all parties involved [7].

Derangements of the pulmonary/respiratory system have long been recognized by emergency providers as an indicator of serious illness and of the potential need for prompt intervention. Patients who present to the emergency department (ED) in respiratory distress appear extremely ill and receive rapid attention, in many cases leading to intubation and the use of mechanical ventilation. When caring for a patient with end-of-life/terminal dyspnea, however, for whom these aggressive interventions may be misaligned with patient's goals of care, the necessity for rapid treatment is no less imperative. In these situations, a focused and patient-centric plan coupled with an empiric approach to symptom management is necessary. This chapter will present a structured approach to the management of dyspneic patient at the end of life whose goals are not purely curative and for whom comfort and quality of life are of primary importance. As emergency providers are well aware, responding to acute symptomatology often requires treatment prior to definitive diagnosis, and the management of terminal dyspnea is no different. In some instances, however—namely, those with reversible causes—diagnosis is worth pursuing, and those instances will be discussed herein.

Neurophysiology

The pathophysiology of dyspnea is complex and remains poorly understood compared to other common clinical phenomena such as pain or nausea. The best current evidence counters the traditional model of dyspnea as a singular entity, instead suggesting multiple neurophysiologically distinct afferent pathways each replete with a unique subjective experience and a different set of predisposing stimuli [8, 9]. To illustrate, one such multifaceted model subdivides dyspnea into (1) air hunger, which is the urge to breathe characterized by an increased ventilatory drive secondary to hypercapnia; (2) increased work of breathing, associated with exhaustion due to effortful breathing; and (3) tightness, a sensation most associated with bronchoconstriction and asthma [10]. While the details of this particular multidimensional model of dyspnea are beyond the necessary scope of knowledge for the emergency provider, it is worth noting that data will continue to emerge on these discrete neurologic pathways, with potential implications for specifically targeted therapeutic options in the future. It also highlights the need for careful appraisal of the literature concerning dyspnea and potential for conflicting study outcomes, as the majority of evidence to date is based on the assumption of a single unified perception of dyspnea.

A more practical understanding of dyspnea as it relates to oncologic etiologies focuses primarily on the brainstem respiratory complex and its relation to the most common variant of dyspnea, air hunger [11]. Through direct action on medullary chemoreceptors, $PaCO_2$, PaO_2, and pH act to regulate respiratory drive by modulating both rate and effort [12]. When an insult causes disruption in homeostasis of any of these variables, an appropriate motor response is elicited to correct this imbalance. The end result of these physiologic insults, whether they be mechanical, metabolic, or neuromuscular, is often a failure to match ventilation with brainstem-mediated respiratory drive. Once this mismatch occurs, the patient develops a sensation of breathlessness and air hunger, which may then exacerbate the predisposing condition through increased metabolic demand. Anxiety and fear, sensations which both precipitate *and* are exacerbated by dyspnea, are cortically mediated (primarily limbic and paralimbic) and are distinct from those initial sensations mediated by the brainstem respiratory motor drive [13]. This neurologic distinction allows for multiple therapeutic approaches to be discussed.

Etiology and Prevalence

Dyspnea is widely prevalent in advanced cancer, with a marked increase in symptoms as patients near the end of life [4]. Furthermore, dyspnea is both commonly present in advanced cancer patients presenting to the ED and a predictor of death in this population [14]. While primary lung cancer conveys the highest risk of all malignancies for developing shortness of breath—affecting up to 84% in one large cross-sectional study—all primary cancers are associated with some increased incidence of dyspnea [3, 15]. There are many specific conditions associated with respiratory compromise which disproportionately affect patients with active malignancies. Below is a partial list of these diagnoses with particular emphasis on cancer-related etiologies and common comorbid conditions. Many are reversible, and these will be explored individually later in this chapter [16].

- Airway obstruction: foreign body/aspiration and tumor burden
- Anaphylaxis and angioedema
- Asthma/reactive airway disease
- Anemia: blood loss, nutritional deficiency, and chemotherapy-induced
- Behavioral/emotional: anxiety and panic attack
- Chronic obstructive pulmonary disease/emphysema
- Deconditioning/cachexia/muscle weakness
- Decreased cardiac output: myocardial ischemia, arrhythmia, tamponade, and hypovolemia

- Decreased chest wall compliance: hepatosplenomegaly, ascites, obesity, and tumor burden
- Diaphragmatic/respiratory muscle weakness: neuromuscular disorders and fatigue
- Metabolic acidosis: renal failure, sepsis, and toxic ingestions
- Pneumonia
- Pneumothorax
- Pulmonary edema/congestive heart failure
- Pulmonary effusion: malignant and infectious
- Pulmonary embolism
- Pulmonary hypertension
- Pulmonary fibrosis/interstitial lung disease: autoimmune, environmental, and secondary to radiation or chemotherapy
- Pulmonary receptor stimulation: environmental irritants
- Ventilation/perfusion mismatch

Complicating diagnosis and treatment, most patients will present with multiple, coexisting etiologies of dyspnea; a study of 100 advanced cancer patients revealed a median of 5 different abnormalities that could have contributed to their shortness of breath [17]. The most frequent cause for symptoms in this cohort was a direct pulmonary pathology related to disease progression; this was followed by treatment-related pathologies secondary to chemotherapy or radiation and then by nonmalignant etiologies such as underlying chronic lung disease. There were, in up to 30% of patients with dyspnea and advanced cancer, no clear identifiable causes for their dyspnea [17].

Evaluation

Arrival in ED/History

Evaluation of the undifferentiated patient with respiratory distress may be challenging in the emergency setting. Frequently, providers face an acutely unstable patient with limited access to complete medical history. Patients may arrive initially unaccompanied by family or caregivers to provide historical context to the hospital visit. In these situations, management should proceed as with any other emergency patient: with focus on stabilization of the airway, breathing, and circulation, as represented through legal advance directives. In many states, the increasingly utilized POLST (Physician Orders for Life-Sustaining Interventions) advanced directive contains the only legally recognized out-of-hospital Do Not Intubate (DNI) order and can provide critical guidance in the early management of unstable patients with advanced cancer. If the situation arises in which an intervention was made—such as endotracheal intubation—and it later becomes clear that this was misaligned with the patient's stated goals of care, there is no legal or ethical barrier to withdrawing these life-sustaining treatments in the ED [18].

Physical Exam

There are many elements of the physical exam in the dyspneic cancer patient which can aid in both prognostication and diagnosis. As patients may be unable to communicate either secondary to their chronic disease process or from their dyspnea, exam findings must be used to guide acute medical management. Classic signs associated with respiratory distress include gasping, accessory muscle activation, tachypnea, shallow respirations, and poor air movement on lung auscultation. Facial expressions should also be noted, as grimacing may suggest pain or discomfort from dyspnea [16]. Family members or caregivers may be especially helpful in this regard, as they may be more skilled at distinguishing specific nonverbal cues or changes from baseline appearance [19]. Chest auscultation for abnormal breath sounds may also guide management—diffuse wheezing may suggest an obstructive process such as asthma/COPD, while bibasilar or focal rales may be more indicative of pulmonary edema or pneumonia. Stridor is concerning for upper airway obstruction or allergic reaction. A focal or asymmetric decrease in breath sounds could indicate pulmonary effusion, pneumothorax, or hemothorax. Distant cardiac sounds or a cardiac rub is concerning for pericardial effusion. In patients with notable skin pallor, anemia may be contributing to dyspnea, while peripheral cyanosis would suggest a more significant hypoxic state. Abdominal distention may represent underlying malignant ascites, which may cause restriction in lung expansion and subsequent respiratory distress. Peripheral edema, especially a change from baseline, may indicate worsening heart or renal failure, while asymmetric extremity edema may be concerning for deep vein thrombosis and pulmonary embolism.

There is prognostic value in certain physical exam findings at the end of life. For example, the inability to clear oral secretions, colloquially known as a "death rattle," has been associated with a median time from onset to death of 23 h [20]. Other physical exam findings to guide expectations include respirations with mandibular movements (median time 2.5 h), extremity cyanosis (1 h), and inability to palpate radial pulse (1 h) [20]. A retrospective chart review of advanced cancer patients revealed the following historical and vital sign abnormalities as predictors of death within 2 weeks: triage respirations >28 (RR 12.7), pulse >110 (RR 4.9), history of uncontrolled progressive disease despite treatment (RR 21.9), and history of metastatic disease (RR 3.9) [21].

Laboratory Studies

There is no strong evidence to guide the decision to send laboratory studies in the acute emergency setting for the terminal cancer population. Consider sending labs if they could provide diagnostic clues which will lead to action consistent with the patient's stated goals. In some patients, the placement of an intravenous line alone is an unwelcome burden.

If mechanical ventilation is an option, assessment of $PaCO_2$ may be of clinical utility. If the patient wishes to receive blood transfusions, a complete blood count should be checked, along with a type and screen. While lactate levels have been shown to correlate with mortality and thus could theoretically be used as a prognostic tool, a study on patients with advanced cancer found that arterial blood gas could not help differentiate between patients who died imminently and those who did not [21, 22].

EKG

An electrocardiogram is a noninvasive intervention which provides rich diagnostic information and minimal patient burden. An EKG can provide diagnostic clues to indicate myocardial infarction, dysrhythmia, pericarditis/myocarditis, pericardial effusion, pulmonary embolism/heart strain, electrolyte abnormalities, or digoxin effect. In the absence of any compelling reason not to, or if refused by the patient, obtaining a 12-lead EKG should be part of the ED evaluation of the dying patient with dyspnea.

Imaging

Chest X-ray is similar to the electrocardiogram in terms of great diagnostic value compared to minimal burden. Common etiologies of dyspnea may be diagnosed rapidly in the emergency setting with chest radiography: pleural effusions, pneumothoraces, and pulmonary infiltrates/edema are all easily identifiable and may allow for target therapies to relieve symptoms. For patients with limited functional status, portable films may be shot at the bedside. As an adjunct, or even a potential replacement, for chest radiography is bedside ultrasound. Emergency physicians are becoming more adept at using ultrasound as a diagnostic tool and as a procedural aide, and the noninvasive nature of the modality allows for high-quality images to be collected with a minimum burden to the patient. Recent studies have shown that thoracic ultrasound can differentiate between cardiac and pulmonary causes of dyspnea and accurately diagnose free or loculated pleural effusions, pneumothoraces, and lung consolidations [23, 24].

Generally, there is limited value in computed tomography (CT) for the diagnosis and treatment of dyspnea in terminal cancer patients. While CT represents the gold standard for detection of pulmonary embolus (PE) and therefore should be used if the patient's goals of care and functional status align with PE treatment protocols, this test requires that the patient briefly leave their monitored bed and move to a radiology suite where close symptom management is challenging and onto a flat exam table which may exacerbate dyspnea [25]. Also, since it is reasonable to discontinue or hold anticoagulation for treatment of venous thromboembolism when advanced cancer patients enter the dying phase, it extends that withholding anticoagulation for acute PE is also reasonable; these patients are unlikely to see significant long-term benefit from anticoagulation and are at higher risk for complications [26]. Symptomatic management can and should continue despite the lack of a concrete diagnosis, so if PE is suspected, the decision to pursue advanced imaging should come only after a frank discussion with patient and family about the risks of harm and benefit of the proposed treatment course.

Cardiac Monitoring/Telemetry/Vital Signs

Cardiac monitoring provides real-time information to providers and can also help to identify transient dysrhythmias. However, it also provides a noisy and oftentimes fear-producing distraction for patients and their families. Unless there is a clear and convincing reason to keep patients on cardiac monitoring, consider changing alarm limits, turning off in-room monitor screens, or removing the patient entirely to minimize physical barriers between patient and family. Vital sign abnormalities should be expected in the dying patient, and unless the rapid identification of these vital signs will make a meaningful impact in patient care, it may be best to keep them off. This will allow the family to focus on their loved one without distractions and remind providers that treatment of the patient should come before treatment of vital sign abnormalities in this population.

General Management

There exist two approaches to the alleviation of dyspnea, as there are with most acute symptoms: One approach is to correct the underlying disorder responsible for the insult in physiologic hemostasis. For example, this may include the drainage of a symptomatic pleural effusion or pericardial effusion. It may involve provision of supplemental inhaled oxygen to a hypoxic patient or bronchodilators to an asthmatic. In the acute setting, however, diagnostic uncertainty exists, and a direct approach is not always possible. And in some scenarios, the medical treatment necessary for correction of a primary insult may come with an unacceptable side

effect profile or burden to the patient being treated. In these situations, a second approach is necessary to alleviate dyspnea by interfering with the downstream cortical pathway. This is not a departure from standard emergency practice—many patients present to the ED with undifferentiated pain or nausea, which requires prompt symptomatic treatment prior to availability of diagnostic testing.

Opioids

The general approach to nonspecific, terminal dyspnea primarily consists of systemic opioid administration. Opioids are safe, effective, and largely predictable and fall well within the comfort zone of the emergency provider. The majority of laboratory and clinical trials to date suggest a benefit of opioids for the treatment of symptomatic breathlessness in advanced illness [11, 27]. But similar to the pathophysiology of dyspnea itself, the exact mechanisms by which opioids exert their influence and alleviate dyspnea are not entirely understood. Leading theories based on current experimental evidence indicate that opioids likely function to modulate the effect of chemoreceptor-activated central respiratory drive on actual ventilation rate and effort [28]. By reducing this reaction to insult and the subsequent compensatory physiologic changes, an increased subjective tolerance may be reached. In addition, the established presence of opioid receptors in bronchial epithelial cells indicates a potential function in both central feedback and local inflammatory response [29, 30]. Finally, there exists a strong emotional component of anxiety which is commonly reported alongside dyspnea and acts to exacerbate the subjective experience. Though it is unclear whether there exists a direct or indirect effect, opioid administration has been shown to measurably decrease reported anxiety in dyspneic patients [30].

In 2011, Banzett and colleagues performed a well-controlled randomized trial using morphine for the relief of dyspnea [31]. This study artificially stimulated air hunger by limiting minute ventilation in healthy patients while inducing hypercapnia. Using patient-reported dyspnea scores on the validated VAS as their primary outcome, IV morphine was compared to IV saline with a significant benefit in both dyspnea scores and anxiety in the morphine study arm. While this study was performed on young and healthy subjects and therefore is less representative of the typical cancer patient, it provides insight into the mechanics of dyspnea and offers valuable data from a controlled environment.

Larger analyses of clinical data have also revealed similar findings. In a 2015 systematic review, opioids demonstrated modest effectiveness for dyspnea in cancer patients. Most of the included studies evaluated morphine. The quality of the included studies varied, with only 4 of the 14 including a placebo arm [32].

The choice of opioid medication for the relief of breathlessness is based on provider preference and departmental availability, similar to the treatment of pain. The literature bears this to be true, as dyspnea studies often use different, but generally equivalent, opioid regimens. There have been clinically significant results shown in trials with oral dihydrocodeine [33], oral hydromorphone [34], IV morphine [35], and oral morphine [36] and multiple studies on subcutaneous morphine [37]. Renal dysfunction has been cited as a justification for caution in morphine administration secondary to the theoretical risk of limited renal clearance of toxic metabolites, although the data for this is not robust [38]. Fentanyl has no clinically significant active toxic metabolites and may be effectively used if there is provider concern [39].

Route of administration should be based on patient-specific parameters; in patients with intravenous access, for whom peripheral IV placement is within their established goals of care and does not represent and unwelcome burden, IV administration is straightforward and rapid. These medications can also be delivered subcutaneously in patients without IV access with minimal discomfort and may also be given orally for those patients able to safely swallow. As was described earlier, there is no strong data to support the use of nebulized opioid formulations, despite the potential for benefit given the known presence of local opioid receptors within lung epithelial cells [30]. However, it has been suggested that many of these nebulized trials have failed to show a difference against placebo due to the fact that nebulized saline could also be an effective treatment modality [27]. Finally, there have been no randomized controlled trials on formulations other than morphine for nebulized delivery, so additional investigation must be performed prior to ruling out nebulized opioids altogether [37].

In terms of dosing and escalation, providers should treat opioid administration for dyspnea similar to pain, by giving a reasonable starting dose and reassessing symptom progression in 10–15-min intervals, up-titrating as needed [16]. Recent prospective trials have used mean doses of 2.5 mg of PO hydromorphone (equivalent to 0.4 mg IV) and 9.4 ± 8.8 mg of PO morphine (equivalent to 0.8 mg IV) to achieve a desired level of patient comfort. Reasonable starting doses for opioid-naïve patients, therefore, should be approximately 1–2 mg IV morphine equivalent or 0.2–0.4 mg IV hydromorphone. If symptoms are unchanged after 10–15 min, consider re-dosing an equivalent or increased amount. If symptoms are improved, but not fully controlled, consider giving another 50% of the starting dose, and continue to reassess. Be aware that higher doses may be necessary in patients who are opioid tolerant; many advanced cancer patients will be on chronic standing and/or breakthrough opioids for chronic pain. In these situations, start by administering approximately 10% of the patient's total daily

opioid dose. For example, if a patient takes 15 mg of oral morphine every 4 h around the clock, their total daily dose equals 90 mg. An appropriate initial dose would be 9 mg PO morphine (equivalent to 3 mg IV). If the patient is taking multiple formulations of opioids, a conversion table should be employed to ensure safe dosing practices. Complicated dosing or high-dose opioid regimens should warrant a consultation with the palliative care service, if available.

Measure improvement in dyspnea through direct patient report, if possible. Again, similar to pain management, the patient's subjective experience of their symptoms is the best indicator of improvement. A visual analog scale (VAS) is usually used for these purposes in both research and clinical use. However, as patients near the end of life are oftentimes unable to effectively communicate, providers will often be forced to rely on elements of the physical exam and family gestalt to gauge response to treatment. It has been suggested to use simple "yes/no" questioning for symptom relief in patients struggling to communicate, as many patients who are unable to provide a scaled response to symptom improvement are still able to indicate yes/no responses [19]. There has also been a respiratory distress observation scale developed for these clinical scenarios, which involves heart rate, respiratory rate, degree of restlessness, accessory muscle use, end-expiratory grunting, nasal flaring, and a "look of fear" [40]. These tools are necessary to prevent undertreatment of a patient's symptoms due to communication challenges.

It is important to consider the potential side effects associated with opioid administration, chief among them being constipation. For this reason, any patient placed on scheduled opioid treatment should be managed expectantly with a bowel regimen. Common prophylactic regimens include a stool softener (e.g., docusate, polyethylene glycol, magnesium) with a stimulant laxative (e.g., senna, bisacodyl) [41]. Other side effects to consider include nausea, vomiting, sedation, pruritus, and allergy/anaphylaxis. These can be managed supportively.

There is understandable hesitation on the part of emergency physicians when considering the use of opioids in patients with dyspnea. In sufficient doses, opioids can lead to respiratory depression and even apnea, so administering these medications to a patient with respiratory compromise can seem dangerous. Fortunately, there is evidence to support the safety of these agents in cancer populations suffering from dyspnea, particularly those patients at the EOL. In several small prospective observational studies, mostly comprised of patients with advanced cancers, carefully administered opioids, even when given to opioid-naïve patients, did not result in clinically important respiratory depression or hypercapnia [42–44]. Furthermore, two large observational studies of hospice patients found minimal to no association with opioid usage, dosage, and life expectancy [45]. The key to safe, effective opioid administration, as stated earlier, is to "start low, go slow" carefully targeting symptomatic relief, titrating up doses in appropriate intervals and with appropriate clinical monitoring.

Benzodiazepines

In select clinical scenarios, administration of benzodiazepines may be considered as a second- or third-line pharmacologic agent. The primary indication for this medication is when anxiety appears to be playing a significant role in the patient's discomfort and when other interventions have failed to alleviate symptoms. As briefly stated earlier, there is a physiologic justification for benzodiazepines despite the current lack of strong supporting clinical evidence. In current neurophysiologic models of dyspnea, there appears to be a distinct emotional component of dyspnea, which may be modulated by opioids but may theoretically benefit more from the anxiolysis associated with benzodiazepine administration [10].

There is, however, a very weak clinical evidence base for this intervention with few studies indicating effectiveness. The largest review to date published in 2016 examined 8 independent trials composed of 214 subjects and found no benefit to these agents when compared to placebo or opioids [46]. Compared to placebo, somnolence and drowsiness were observed more frequently in patients receiving benzodiazepines. Surprisingly, when midazolam and morphine were directly compared, morphine was associated with more adverse events.

Given limited evidence for efficacy but without evidence for serious harm when used in small doses, benzodiazepines should be considered as an adjunct to opioids in situations where anxiety appears to be playing a role in symptomatology [47]. A starting dose of lorazepam 1 mg (PO or parenteral) or diazepam 5 mg (PO or parenteral) would be appropriate in most patients.

Corticosteroids

Corticosteroids represent a treatment for certain conditions associated with advanced cancers and should not be applied generally in the same fashion as opioids and benzodiazepines. There is limited data on their use, but case studies report temporary symptomatic improvement for specific conditions such as lymphangitic malignant spread and chemotherapy-/radiation-induced pneumonitis [48]. Corticosteroids are the mainstay of treatment for radiation-induced lung injury, typically treated with a taper starting with 60–100 mg of daily oral prednisone [49]. There are also case reports of rapid improvement in dyspnea associated with upper airway tumor

obstruction after administration of steroids, likely secondary to reduction in airway edema [50]. Reported doses include 10 mg IV dexamethasone and 125 mg IV methylprednisolone, administered every 6 h. A recent systematic review found no benefit to steroids in cancer patients with dyspnea, though the quality of the included studies was low, limiting the ability to draw firm conclusions [51]. Significant side effects exist and must be considered. These include hyperglycemia, infection risk, fluid retention, and potential psychomotor agitation [52]. In patients with life expectancies of days to weeks, however, long-term side effects are less concerning and therefore should be balanced against potential benefit.

Supplemental Oxygen

Supplemental oxygen is often reflexively administered to patients presenting to the ED with dyspnea, particularly those patients suffering from hypoxia. While oxygen has been demonstrated to improve the QOL and longevity of patients with severe COPD, its use in patients with dyspnea at the EOL is more controversial [53, 54]. In one large randomized trial of patients with advanced illnesses and dyspnea, about 15% of whom had cancer, home oxygen resulted in no symptomatic improvements when compared to room air [55]. Surprisingly, in a prospective cohort study of patients admitted to a palliative care unit with advanced cancers, hypoxia and dyspnea showed little correlation. Furthermore, patients in this study had more dyspnea relief with opioid rather than oxygen administration [42]. As hypoxia is likely just one of the many factors contributing to dyspnea at the EOL, these results are somewhat predictable. Regardless, certain oxygen delivery devices like nasal cannula are minimally burdensome, so a time-limited trial in hypoxic, dyspneic patients can be considered, even those endorsing comfort-oriented goals. More caution should be used, however, when applying more burdensome devices like a non-rebreather mask, if the goals are comfort-oriented, as this may actually contribute to discomfort without clear evidence of efficacy.

Noninvasive Ventilation (NIV)/Mechanical Ventilation

NIV has been well studied and its efficacy well demonstrated in patients with CHF and COPD [56]. In recent years, this tool has been applied to a broader range of patients, even those with advanced cancers. A randomized trial evaluated the use of NIV when compared to oxygen (via venture or non-rebreather mask) for patients with advanced cancers presenting with acute respiratory failure. Patients receiving NIV had greater improvements in dyspnea scores and needed less opioids; however, about 10% of patients randomized to NIV discontinued therapy secondary to issues like mask intolerance (compared to none in the oxygen group). Mean survival was the same in both groups, 4–5 days; however, seemed to favor the use of NIV in those patients with concomitant hypercapnia [57]. In an observational study of patients with advanced cancer and respiratory failure, over half of patients treated with NIV actually survived their acute illness and were discharged alive from the hospital [58]. In a cohort of lung cancer patients receiving NIV, predictors of mortality included a new lung cancer diagnosis or progressive disease, multiorgan failure, and need of NIV as the first-line therapy for respiratory failure. The 1-month mortality for this small cohort was approximately 40% [59]. These studies suggest that for select patients with advanced cancer and a potentially reversible cause of acute dyspnea/respiratory failure, NIV can be a useful tool that improves symptoms and meaningfully prolongs life. In other patients, however, particularly those with respiratory failure secondary to progression of underlying disease, NIV may artificially prolong dying and worsen suffering at the EOL [60]. Prior to initiation of this therapy, it is recommended that clear, time-specific goals be established with the patient and/or key decision-makers. For example, if there is no marked improvement in the patient's mental status and/or the mask seems to be causing discomfort in the next 24 h, NIV should be transitioned off, and opioids used exclusively to alleviate dyspnea.

Intubation is often considered, particularly in the ED, in advanced cancer patients with dyspnea and respiratory failure. Counseling patients and their families about the risks and benefits of this invasive intervention is critical. A recent study of cancer patients admitted to the ICU requiring ventilatory support demonstrated the importance of contextualizing the respiratory failure within a broader understanding of the overall illness. In the subgroup of patients with relapsed cancer and poor performance status (poor baseline function), hospital mortality was high, approaching 90% [61]. Trends over the last 10 years suggest more patients with metastatic cancer receiving mechanical ventilation, despite no changes in outcomes over this time frame [62]. Patients and families should be counseled that the use of mechanical ventilation is very unlikely to meaningfully prolong life in patients dying from an advanced cancer and is likely to lead to a burdensome death within the ICU setting.

High-Flow Nasal Cannula

High-flow nasal cannula (HFNC) has emerged a useful tool in managing hypoxemic respiratory failure in select patients. Heated and humidified oxygen is delivered at higher rates

than would be possible via a traditional nasal cannula system. Unlike other advanced modalities like NIV and a non-rebreather mask, HFNC theoretically leads to improved comfort as patients can still communicate and eat and drink while wearing the device. In patients with respiratory failure and electing DNR/DNI status, HFNC seems to improve oxygenation and decrease the respiratory rate. When compared to other oxygen delivery modalities, however, there is no difference in dyspnea scores or morphine usage [63]. Similar to studies of NIV in patients with advanced cancer, mortality rates in these studies are high, ranging from 40 to 87%. In awake patients still able to engage with loved ones and/or interested in eating and drinking, this tool can be considered.

Management of Specific Conditions

Pleural Effusion

Malignant pleural effusion is a challenging entity in the emergency setting, particularly in symptomatic patients with guarded prognoses. It is a common condition, with an estimated 150,000 cases in the USA annually and a prevalence in advanced cancer of approximately 15% [64, 65]. Most pleural effusions will not become symptomatic until they reach over 500 cc in volume, and they can expand to over 2000 cc in volume. Practice guidelines for malignant effusions have traditionally recommended drainage with bedside thoracentesis, with consideration of pleurodesis—typically with talc—for prevention of recurrence and re-accumulation [66]. Talc pleurodesis, however, requires inpatient hospitalization and surgery, may be distressing and painful, and may lead to further complications including pneumothorax or empyema. Increasingly, indwelling pleural catheter drainage is being employed for either permanent or temporary management of re-accumulation, thus diverting patients away from the traditional and burdensome pleurodesis [64]. Compared to pleurodesis, patients with malignant effusions receiving an indwelling catheter spend fewer days in the hospital near the end of life [67]. Of note, palliative chemotherapy may actually benefit patients with recurrent effusions who have chemotherapeutic-responsive tumors [65]. This does not represent an emergency intervention but should be known when discussing the full range of therapeutic options with a family.

Functional status and patient prognosis should guide treatment, along with patient and family values and goals of care. In general, therapeutic thoracentesis alone is typically recommended in patients with a short expected prognosis or poor functional status, which allows for temporary evacuation of pleural fluid without necessitating hospital admission. Effusions may re-accumulate rapidly within days or slowly, on the order of months. There are no good predictors to help determine which patients are at a higher risk for rapid re-accumulation [64]. The potential for rapid recurrence is an important detail to share with patients' families who may have very different expectations of this procedure. Most, but not all, patients will experience relief in dyspnea following a thoracentesis, but given that dyspnea is multifactorial in advanced cancer, families should also understand that thoracentesis is not necessarily a definitive treatment for an individual patient's symptoms. For those patients with frequent recurrent pleural effusions or for those with predicted longer life expectancies, it may be more appropriate to refer for pleurodesis or tunneled catheter placement.

If performed in the emergency setting, thoracentesis should be done by an experienced provider utilizing ultrasound guidance. A retrospective study on 445 patients undergoing thoracentesis for malignant pleural effusion revealed a 0.97% pneumothorax rate with ultrasound guidance and 8.89% without [68]. Re-expansion pulmonary edema is a known potential complication and may occur if greater than 1.5 L are removed at once, although the incidence of this is uncommon, around 0.5% in a series of 185 cases [69, 70].

Anemia

Advanced cancer patients have a high prevalence of anemia, with studies suggesting up to 70% of these patients live with a hemoglobin concentration below 12 g/dL. While the majority of anemia in this population is of unclear etiology, many are thought to have anemia of chronic disease or nutritional deficiencies, notably of folic acid [71]. In a study aimed at establishing the cause of dyspnea in advanced cancer patients, up to 20% of enrollees were found to have a hemoglobin level which was low enough to have affected tissue perfusion [17]. In these situations, transfusion should be considered. Major elements impacting this decision include prognosis, functional status, and goals of care. There are risks and burden associated with transfusion, including additional time spent in the hospital, necessarily placement of intravenous access, and the risks of transfusion reaction, infection, or fluid overload. A prospective study of outpatient palliative care patients with cancer found that by using a transfusion cutoff of 8 g/dL, patients had a significant improvement in both self-reported dyspnea and fatigue, but these effects began to decrease approximately 2 weeks after transfusion [72]. The decision to transfuse should be left up to the treatment team in conjunction with the patient and family, though they should be aware that the subjective benefit in dyspnea relief is likely temporary and does carry some limited risk.

Oral Secretions

As death approaches, secretions pool in the posterior oropharynx, and patients become too weak to swallow or clear them. Anticholinergic agents are commonly used to address the noisy breathing that many patients experience as a result. Most patients are unconscious at this point and thus unlikely to be bothered by what is known as the "death rattle" [20]. Family members, however, can find the noise distressing, so treatment is often considered. Unfortunately, there is a lack of high-quality evidence on this topic to guide management. In a 2014 systematic review of interventions for noisy breathing near the end of life, only one small study was placebo-controlled, and the authors could find with no clear benefit found to any treatments evaluated [73].

For patients with intravenous access, glycopyrrolate 0.2 mg IV or atropine 0.1 mg IV can be administered. For those without IV access, drops of atropine 1% ophthalmic solution can be given by mouth [74]. More important than medication choice, however, is educating family and caregivers that this is a normal part of the dying process unlikely to be distressing to the patient. It is also an established prognostic sign that life expectancy is likely hours to days.

Tumor Burden

Lymphangitic carcinomatosis (LC), a condition involving hilar/mediastinal lymphatic inflammation secondary to malignant spread, affects between 6% and 8% of patients with intrathoracic metastases with the most common underlying primary tumors being breast, stomach, and lung [75]. LC manifests as nonspecific, nonproductive cough with associated dyspnea and may be definitively diagnosed by CT scan or bronchoscopy/biopsy [76]. As a late finding in advanced cancer, it carries a poor prognosis, with 50% survival at 3 months after first respiratory symptom. Corticosteroids have a palliative role by decreasing inflammation and should be considered in patients who carry this diagnosis [48]. In certain cases, palliative chemotherapy may also be offered and may give temporary improvement in symptoms over time.

Palliative Extubation

Establishing goals of care can be a time-intensive and arduous process. Oftentimes, a patient presents profoundly dyspneic to the ED alone or with EMS and with no ability to communicate their wishes about the use of life-sustaining treatments (LST). In these situations, unless emergent airway management appears futile, patients will be intubated and placed on mechanical ventilation. After medical stabilization, when it is possible to clarify a patient's wishes with family or supporting documentation, it may become clear that the patient's goals are inconsistent with mechanical ventilation. Appropriate management in these situations will vary—some families prefer to wait until they leave the ED into a more controlled environment (a hospital room or on a palliative care floor) prior to withdrawal of mechanical ventilation. In other situations, the emergency provider may withdraw support in the ED.

There may be hesitation on the part of the healthcare provider regarding the ramifications of withdrawal of LST in the ED. A public health survey of medical attending physicians in 1993 revealed that only 43% agreed that "there is no ethical difference between forgoing a life support measure and stopping it once it has been started" [77]. But from both an ethical and legal standpoint, there is no difference between these two actions [78]. The ethical principle of *autonomy*, which dictates that a patient has the right to make his or her own decisions, must be honored. Providers should seek documentation of the patient's wishes in the form of advance directives like a living will or POLST. When written directives are not present, surrogate decision-makers can use the principle of substituted judgment to make decisions that they feel would be in the best interest of the patient [79].

Prior to withdrawal of mechanical ventilation, family should be informed about the prognosis and potential outcomes following withdrawal. There is a common expectation that death is imminent after endotracheal tube removal, so appropriate counseling on the range of outcomes should be given. In a small cohort of patients terminally extubated in the ICU, mean time to death was 2–3 hours [80]. In another study of mechanically ventilated ICU patients who were terminally extubated, half died within 1 h of withdrawal, with the majority dying within 10 h [81]. Factors that were predictive of an earlier time to death included a high oxygen requirement ($FIO_2 > 70\%$) and the use of vasopressors. Note that over half of this study group had been mechanically ventilated for over 10 days, and therefore these results may not be entirely reflective of the acute/emergency population. While most patients will live minutes to hours, families should be counseled that some can live for days.

Families should be allowed to make any necessary spiritual arrangement. Monitors and unnecessary equipment including blood pressure cuffs and pulse oximeters should be turned off and/or removed. It is best to keep IV access in place for rapid administration of sedatives if necessary.

There is debate about whether patients being extubated should be weaned from mechanical ventilation gradually, allowing the careful matching of opioids to symptoms, or extubated abruptly. In an uncontrolled study, when compared to immediate extubation, weaning seemed to lead to improved patient comfort [82]. If weaning is selected, the amount of pressure support and oxygen should be gradu-

ally decreased over 30 minutes prior to extubation. At the time of extubation, the tube cuff is deflated, and then the tube is removed, followed by cleaning and suctioning of oral secretions.

A dose of glycopyrrolate 0.2 mg IV can be given to minimize respiratory secretions, prior to extubation. As dyspnea is the primary symptom post-extubation, opioids are the first-line agents used during this procedure. Prior to extubation, an opioid should be given. Typical doses of morphine used are 4–6 mg. The goal of palliative medications is to minimize tachypnea and prevent agitation [79]. Families may be concerned with sedative administration, but similar to the management of undifferentiated dyspnea without airway management, provision of opioids after palliative extubation does not appear to have any effect on hastening death [83, 84]. Be available to the family, as they will often have questions during the dying process and may ask for frequent reexaminations of their loved one.

After the patient dies, ensure that the family is able to spend time around the bedside and provide bereavement support as needed.

Summary

Dyspnea in advanced cancer is distressing, complex, and often multifactorial. As patients approach the end of life, dyspnea becomes a common endpoint for multiple disease processes, with many factors simultaneously contributing to a patient's underlying shortness of breath. Many of these patients will seek care in the ED, necessitating emergency providers to have a strong understanding of the pathophysiology and management of terminal dyspnea. Above all, clear and open communication will help guide the diagnostic workup and treatment course for a patient with dyspnea near the end of life. Patient's goals may range from purely symptomatic treatment to aggressive extension of life, and therefore each patient will need to receive truly customized care from the onset of their ED visit.

Fortunately, while the neurophysiology of dyspnea is complex, the treatments are not. Opioids are the clear mainstay of symptomatic management. The proper titration of opioids will often be sufficient to adequately treat dyspnea at the end of life, but in certain situations a patient may require or request more intensive treatment. These interventions range from blood transfusions to noninvasive ventilation to bedside thoracentesis. By developing a keen understanding of the risks, benefits, and long-term outcomes of these interventions, the emergency provider is better able to equip the patient and family with the information they require to decide whether the intervention aligns with their goals and values.

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Cardiopulmonary Resuscitation

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Introduction

Cardiopulmonary resuscitation (CPR) can be a lifesaving intervention; however, the indiscriminate use of CPR among unselected populations, and particularly among those with cancer, confers beneficial outcomes (e.g., survival to hospital discharge) on only a small proportion of patients [1–12]. In the USA, CPR is routinely provided to those suffering cardiac arrest without their consent. Only when patients give caregivers explicit instructions to withhold CPR is it not performed [1, 13, 14].

In 1960, Kouwenhoven et al. [14, 15] first described closed-chest massage, intended for administration to otherwise "healthy patients" with reversible conditions who experienced sudden and unexpected cardiorespiratory arrest. Today, despite the near universal application of CPR, in most cases and particularly among cancer patients, CPR merely prolongs the dying process [2, 12, 16–22]. During the last 15 years, researchers have determined that cancer patients have a particularly low rate of return of spontaneous circulation (ROSC) and survival to hospital discharge (SHD) after CPR [1–11]. SHD rates are substantially better for in-hospital CPR compared to out-of-hospital CPR among all comers. SHD rates for out-of-hospital CPR and in-hospital CPR in an unselected population undergoing CPR are 1–10% and 15%, respectively [2, 16–22], but for cancer populations it is <6% [9, 10]. Even among patients with stage IV cancers who survive in-hospital CPR, the median survival after discharge is only 22 days [23]. Cardiopulmonary arrest is the common final pathway for most terminal diseases, including cancer [9, 10]. Despite the low rates of SHD and short survival after discharge, CPR may be aligned to patient's goals of care. More information is needed to better understand the quality of life for survivors and under what conditions CPR is appropriate.

An increased emphasis on palliative and supportive care for cancer patients improves quality of life [24–26]. Palliative services incorporated in planning and executing therapeutic interventions hold the promise that CPR might be used more selectively. A more selective approach to initiating CPR, incorporating the patient's goals of care, should lead to increases in goal-concordant care.

In this chapter, we discuss how to determine whether CPR is aligned with goals of care among patients with cancer, explore palliative and supportive care resources, and describe CPR outcomes in tertiary cancer centers. We will also examine the issue of family-witnessed resuscitation.

What Outcomes After CPR Are Acceptable to Patients?

Emergency physicians understand that when patients with cancer arrive in the emergency department (ED), many have an inaccurate understanding of their illness and prognosis. Studies show that 69% of patients with stage IV lung cancer and 81% of those with colorectal cancer did not report understanding that chemotherapy was not at all likely to cure their cancer [27]. When asked about CPR, only 2.7% of hospitalized older patients with end-stage cancer or other advanced diseases understood that actual CPR success rates were <10%. Only 11% of these patients could describe more than two components involved in CPR [28].

To determine whether CPR is indicated for ED cancer patients with limited understanding of both their prognosis and CPR, emergency physicians should focus on a patient-centered prognosis (i.e., what patients with serious, life-limiting illnesses would consider good outcomes). In a national survey study of physicians and seriously ill patients, a number of end-of-life items were rated as significantly more important to patients than physicians, including being mentally aware, having made funeral arrangements, feeling that one's life was complete, not being a burden, being able to help others, coming to peace with God, and praying [29]. Furthermore, ≥60% of seriously ill older adults consider inability to "get out of bed" or "rely on a breathing machine

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to live" as equal to or "worse than death" [30]. The vast majority (87%) of seriously ill, hospitalized, older adults express that they would even trade 1 year of a 5-year lifespan to avoid dying in an ICU on life support [31]. Considering prognosis and likely functional outcomes, emergency physicians must determine what patients would consider an acceptable quality of life should they survive CPR.

How Should Emergency Physicians Make Recommendations Regarding CPR?

To make an empathic and goal-concordant recommendation around CPR, integrate the patient's baseline function and values with knowledge of the patient's prognosis. Ask yourself, "In the best-case scenario, would this patient be able to achieve the minimal quality of life worth living for after CPR?" If this answer is a clear "no" or likely outcome would be considered "worse than death" for the patient [30], emergency physicians can confidently make a recommendation against CPR. If the answer is unclear (e.g., the surrogate may not know the minimal quality of life that patient would consider acceptable to live) or likely outcome would be an acceptable quality of life worth living for, emergency physicians can make a recommendation for CPR (Fig. 58.1). The language used to make the recommendation should reflect how the recommendation was made (e.g., "based on what I heard about you, I would recommend CPR"). Emphasize what you will do (e.g., "focus on ensuring comfort"). Consider explaining why you would not recommend certain therapies in the context of the baseline function and values [32].

Palliative and Supportive Care Interventions

The goal of palliative and supportive care is to prevent or treat, as early as possible, the symptoms of the disease, side effects caused by treatment, and psychological, social, and spiritual problems related to the disease or its treatment. Palliative care focuses on the assessment and management of physical and psychosocial distress of patients with advanced cancer as well as family support and advance care planning [24, 25]. Patients make better-informed decisions with less distress when physical and emotional symptoms are controlled [26]. Furthermore, the manner in which physicians communicate about CPR is important. Of patients with advanced cancer randomly assigned to learn about CPR by either viewing a video decision support tool or listening to a verbal narrative, 79% of those viewing the video opted out of CPR, while only 51% receiving a verbal description decided against CPR [34].

Palliative care is not only pertinent to the end of life; rather, it can and should be provided early in the cancer journey. When engaged early, these services improve quantity and quality of life concurrently with the oncologic care model [26]. This model enables supportive/palliative care to be integrated into the collaborative model that exists among surgical, radiation, and medical oncologists as the fourth pillar of comprehensive cancer care. This multidisciplinary approach allows additional consultants the opportunity to participate in care including, but not limited to, pain specialists; psychiatrists for emotional distress, depression, and anxiety; pulmonologists for relief of bronchial obstruction; and psychosocial interventionists for end-of-life issues [9–11, 24–26]. Incorporating end-of-life education into the day-to-day management of these patients is essential.

Comprehensive Cancer Centers

In one comprehensive cancer center, between the periods 2002–2007 and 2008–2012, rates of ROSC after CPR showed small and statistically insignificant improvements, while SHD outcomes did not change [35] (Fig. 58.2). Any trend toward improved ROSC outcomes that may exist could result from improvements in CPR quality [36, 37].

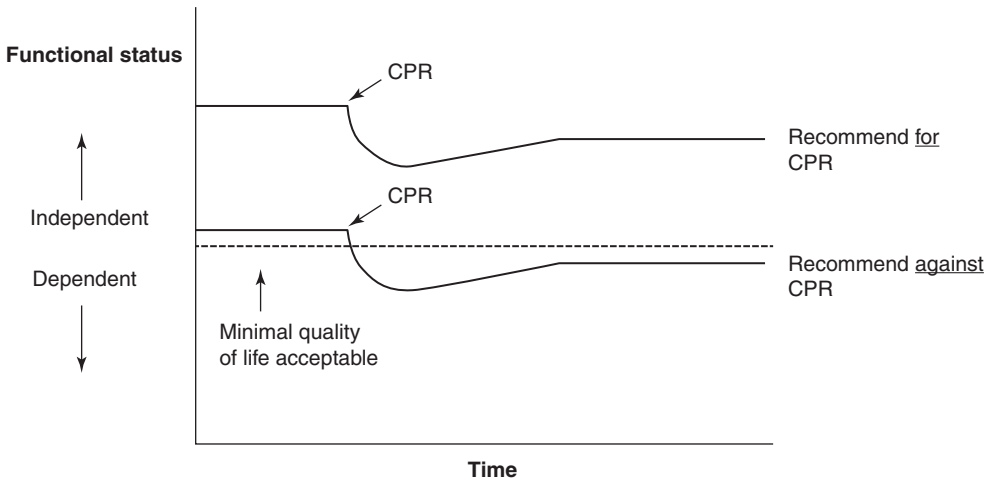

Fig. 58.1 CPR recommendation based on quality of life acceptable to patients. (From Ouchi et al. [33], with permission Elsevier)

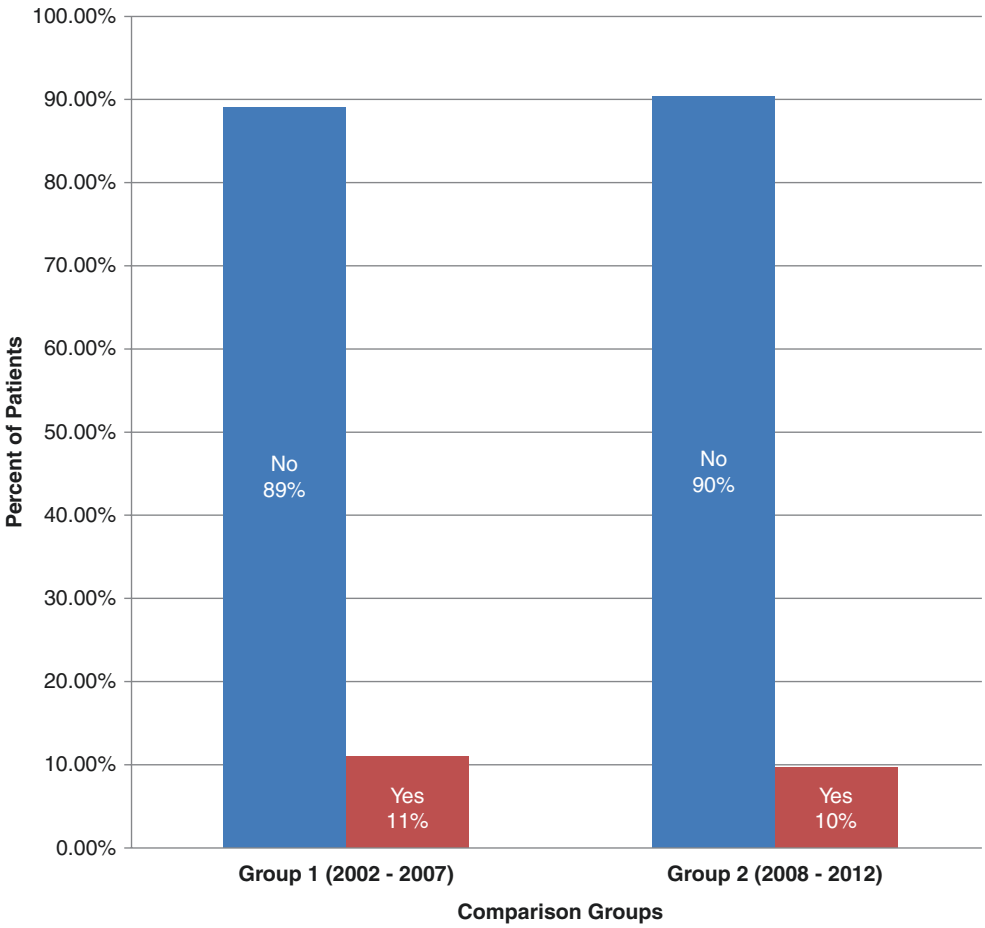

Fig. 58.2 Survival to discharge among 126 cancer patients undergoing cardiopulmonary resuscitation (CPR) in a comprehensive cancer center comparing group 1 (2002–2007) and group 2 (2008–2012). (From Miller et al. [35] with permission SpringerPlus [CC by 4.0])

The lack of improvement in SHD may suggest that CPR in cancer patients continues to be performed on an unselected cancer population, rather than being targeting toward subsets of cancer patients who are more likely to receive benefit.

Reisfield et al. [11] reported in a 2006 meta-analysis that among 1118 patients with cancer receiving CPR, the rate of SHD was 7.1% among those with solid tumor vs. 2% for those with hematologic cancer. Consistent with these data, Hwang et al. [10] reported that during 2000–2002, of 41 cancer patients receiving CPR in their ED, only 6 of 33 patients (18%) with solid tumors and 1 of 8 (13%) with hematologic malignancies were ultimately discharged alive to another facility.

Future research could identify the specific type(s) of cancer that could benefit from CPR. End-of-life and advanced care planning may contribute to improved outcomes of CPR by allowing those terminally ill to avoid ineffective terminal interventions [38]. Improved advance care planning communication and/or documentation and family education can be exploited to improve CPR outcomes in both cancer and noncancer populations. These interventions allow patients and loved ones to avoid transportation to the hospital and CPR [1, 39–41]. As cancer populations increase in the USA, discussions about end-of-life issues will become particularly relevant with regard to economic impact [12].

Family-Witnessed Resuscitation

As noted, survival outcomes measured by improved quality of life are particularly dismal after CPR for cancer patients. Even though the statistics are unfavorable, the decision to resuscitate is often multifactorial. Ideally, end-of-life planning should occur early in the course of treatment so that patient wishes will be clear and based on an adequate consideration of alternate treatment plans. Indeed, planning should occur at all stages of disease.

An important topic particularly relevant to emergency care is that of family-witnessed resuscitation (FWR). According to Boyd, FWR is "the process of active 'medical' resuscitation in the presence of family members [42]. The concept of having family members present during resuscitative efforts was introduced in the 1980s when Foote Hospital in Michigan began promoting FWR [43]. In 1992, Hanson and Strawser presented initial research data on this topic [44]. Twenty years later, in 2000, the American Heart

Association published guidelines recommending that family members be allowed to witness CPR. At the time, there was a lack of research to provide quantitative proof that FWR was beneficial. Another 20 years later, FWR remains the exception in EDs internationally [45].

The question of whether family members or loved ones desire to be present during resuscitation, or whether the emergency physician should consider offering this choice, remains an important policy issue for the ED. Planning and establishing procedures for FWR should occur well before the need to make such decisions arise [46]. We will discuss the pros and cons based on perspectives of all parties that may be present during resuscitation and ethical contexts regarding this issue. We suggest conditions under which FWR should be considered based on a review of existing research.

Perspectives of Family Members

Family members of both pediatric and adult patients play an increasingly larger role as caregivers given the shift in emphasis of care from the hospital to outpatient setting. Oftentimes, they initiate an emergency response in the prehospital setting if their loved one is in distress. Given that family members often participate in treatment planning and day-to-day care, it is not uncommon for them to wish to be present with their loved one during the final moments of life, including resuscitation attempts.

Multiple studies focusing on the attitudes of family members reveal that most prefer to be present during resuscitation when given the opportunity. One 1982 survey assessing bereaved family members in Michigan found that 72% preferred to be present during resuscitation attempts. Other studies confirm the strong desire of family members to be present and that those participating in FWR would recommend the same to other families [47–52].

Despite the strong preference of family members to participate in FWR, the practice remains uncommon. Hospital staff have traditionally excluded nonmedical personnel because witnessing the resuscitation was thought to cause emotional distress. Multiple studies counter this belief and indicate that family members do not suffer negative psychological consequences after witnessing resuscitation. In 2013, Jabre et al. [53] performed a 1-year post-resuscitation study of 408 family members measuring symptoms of posttraumatic stress disorder (PTSD), anxiety, depression, and complications of grief. Family members witnessing resuscitation appeared to suffer less PTSD-related symptoms [53, 54]. A common belief is that participating in FWR allows for a sense of closure after family members witness that everything possible had been done to increase the chance of survival [49, 52, 55, 56].

Perspectives of Healthcare Workers

With endorsement by the Resuscitation Council UK, the European Resuscitation Council, and the American Heart Association, FWR is more frequently performed in the ED. In a survey of 162 UK EDs with a mean patient volume of 47,000 patients per year, 79% (128 EDs) reported allowing adult patients to have FWR [57]. However, FWR is not universally supported by healthcare workers despite studies suggesting that it is beneficial to family members. A survey of 132 ED staff members at a hospital in Singapore found that 80% of doctors and 78% of nurses actually disapproved FWR. Of those surveyed, 32% of doctors and 24% of nurses had received requests from relatives to be present during resuscitation within the past 6 months [58]. Another survey of 100 healthcare professionals at an academic medical center in the USA showed a contrasting result, in that the majority of staff members (77%) were in favor of allowing FWR [59].

Attitudes of healthcare workers toward FWR differ by discipline, patient age, and practice environment. Nurses are more open to FWR than doctors, and family members tend to approach a nurse rather than physician asking permission to witness resuscitation of their loved one [60, 61]. Those caring for younger patients and their families are generally more positive toward FWR. One-third of pediatricians surveyed would allow family presence during CPR, and almost two-thirds with FWR experience would allow this to happen again. In a study comparing pediatric vs. adult pulmonologists, pediatric pulmonologists were far more accepting of FWR [62]. The nature of pediatric care may allow staff to be more accepting of FWR as a right for parents who are legal guardians for their children [63]. A small South African qualitative study revealed that ED staff disliked FWR as they believed it to be harmful for the witnesses as well as a threat to the staff [45].

Practice environment also influences the attitudes of healthcare workers. Staff at urban hospitals are less supportive of FWR than staff at suburban hospitals [64]. Macy suggests that logistics may play a role given that urban hospitals may have inadequate resuscitation space per patient volume. Urban hospitals have smaller staff/patient ratios which may cause staff to feel that family members' presence is a distraction. This study found that patient/personnel ethnicity had no significant effect on overall attitudes toward FWR by medical staff [64]. A cross-sectional study conducted at an American community hospital suggested that critical care nurses who had experience FWR had a trend toward more positive attitudes about the benefits and outcomes of FWR, though the findings were not statistically significant [65].

In general, healthcare professionals opposing FWR express a common concern that witnessing a loved one

undergoing aggressive resuscitation predisposes family members to additional psychological burden [63]. Staff report that witnessing resuscitation may cause family members to suffer flashbacks and other signs of posttraumatic psychological trauma. The reality of what may occur during resuscitation differs than what is usually depicted in movies or on television, and nonmedical personnel may not be mentally prepared to witness a real resuscitation.

A second concern expressed by many healthcare workers is that FWR negatively impacts staff performance. The presence of family members may cause additional stress to healthcare workers, especially those less experienced with code blue situations [66]. Resuscitation is a stressful event, and coping mechanisms, such as humor or detachment from a patient, may certainly be deemed inappropriate by family members. Unrealistic expectations may also exist as family members are not expected to understand resuscitation procedures and may interfere or interrupt resuscitation efforts. Resuscitation may also be inappropriately extended beyond usual time limits based on family presence. An increase in potential for litigation is also cited as an issue given that relatives in the room may be at risk for needle sticks or being injured by a piece of equipment [67, 68]. These findings contrast with the result of several other studies [54, 65].

Given these concerns, most healthcare workers recommend FWR in a controlled setting with protocols in place and specifically trained personnel to accompany family members. Hospital staff would also require additional training which would add to hospital expenses [69, 70]. After receiving education, it is interesting to note that in some studies, staff felt that witnessed resuscitation may indeed lessen the risk of lawsuits and complaints given that family members witnessed firsthand that everything was done for their loved one. Communication about the death of the relative was also found to be easier [58, 63, 71, 72].

Perspectives of Patients

Only 10–15% of patients receiving CPR following cardiac arrest in the hospital survive to be discharged. Therefore, fewer studies exist which examine FWR from a patient perspective. Albarran performed face-to-face interviews with 21 resuscitation survivors, and although the study was statistically insignificant, it suggests that patients who survive resuscitation favor having family members present [73]. Patients would like the opportunity to be asked to approve FWR and were not as concerned about confidentiality issues. Another pilot study by Robinson et al. consisting of three patients surviving resuscitation reported that their confidentiality and dignity were not compromised by FWR [71].

Ethical Considerations

Patients are rarely asked about their preference for family-witnessed resuscitation when preparing advanced directives. The lack of documented consent creates medicolegal implications for FWR because of the potential for breaching patient confidentiality. Acceptable guidelines for pediatric patients do not transfer to adults, given that family members have no legal rights to care for their adult relatives. For adults, permission must be granted from the patient before discussing medical care with relatives. Even if a patient is unconscious, these rights are still present; thus, an assumption cannot be made that all patients would give automatic consent for FWR [63]. Consequences must be considered if a patient survives the resuscitation and is not happy with the decision, though concerns regarding litigations from FWR have not been demonstrated [74].

Guidelines

When considering FWR, the interests of patients, family members, and staff must be taken into consideration, and this is difficult during an emergency situation. Optimally, FWR should be discussed with patients prior to potential resuscitations, e.g., during advance directive planning. If a hospital decides to incorporate FWR, it is recommended that an ED-specific protocol be established. Training of specific ancillary staff should occur so that a qualified staff member can accompany the relative at all times during the resuscitation. The role of this staff member will be to debrief the loved ones prior to entering the resuscitation room, to answer questions during the resuscitation, to escort the relative out of the room if necessary, and to help debrief the relative after resuscitation. Education is desired for the multidisciplinary resuscitation team on what to expect with FWR so that any fear or apprehension can be addressed. If a protocol for FWR is in place and staff are educated, they will less likely deny family member requests to be with their loved one during resuscitation, and family members can be allowed near or even touch their loved one during the process with less concern interfering with resuscitation procedures [69, 75].

Conclusions

In this chapter, we have reviewed the literature pertaining to CPR on patients with cancer. To improve the current status, more teaching of palliative and supportive care to maximize quality of life concurrently with disease-oriented therapies is needed. Despite well-intentioned resuscitation efforts over the last 40 years, the survival outcomes for those with cancer particularly metastatic cancer have not improved [11, 38,

41]. FWR should be considered in the ED; however, the ultimate impact of FWR on family members and loved ones remains uncertain.

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Palliative Surgery

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Caitlin Hodge and Brian Badgwell

Case Study

A 68-year-old woman presents to the emergency department with progressive nausea, vomiting, vague abdominal pain, and weight loss. She reports that her last bowel movement was 2 days ago and that she has lost 20 pounds in the past few months. On exam, she appears cachectic and jaundiced. Her vital signs are stable. Her abdomen is distended and tympanic. X-rays show dilated loops of bowel with air-fluid levels. A CT scan reveals a 5 cm pancreatic head mass and concern for liver metastases. Labs reveal a total bilirubin of 14 and a normal white count and lactate. She can climb two flights of stairs without difficulty.

IVs are placed and fluids are started. An NG tube is placed, which returns bilious output. Her abdominal discomfort improves after NG placement. She is admitted to the hospital for further work-up and resuscitation. An endoscopic ultrasound and ERCP are performed. Biopsies are taken, which confirm the diagnosis of pancreatic adenocarcinoma. Management options for her symptoms resulting from gastric outlet and biliary obstruction are discussed. After thorough discussion of risks and benefits, it is determined that her primary goals are to return home and to start chemotherapy. She then undergoes successful biliary stent placement followed by laparoscopic gastrojejunostomy. She recovers from these procedures and is discharged home.

Introduction

Palliative care, defined by the World Health Organization, is care to improve the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering [1]. Palliative care involves the assessment and treatment of pain and other physical, psychosocial, and spiritual problems. The first distinction that must be made in addressing palliative surgery is differentiating surgical palliative care from medical palliative care. Medical palliative care is the management of symptoms such as pain, nausea, cachexia, delirium, and fatigue. Surgical palliative care can broadly be separated into two main categories. The first is operative palliative surgical care in which surgical interventions are the treatment modality utilized to palliate patients with advanced or incurable illness. Palliative surgery is defined as surgery performed with the purpose of alleviating symptoms and improving quality of life [2]. This form of palliative surgical care is often encountered during surgical consultation or in the emergency department. The second form of palliative surgical care involves nonoperative care and decisions about the appropriate level of care in postoperative or trauma patients with life-threatening conditions or postoperative complications. This form of palliative surgical care is most often encountered in the intensive care unit or postoperative inpatient unit.

The focus of this chapter on palliative surgery will be clinical diagnoses evaluated for potential surgical intervention. Palliative surgical consultation is a frequent occurrence in hospitals that treat cancer patients. Approximately half of all inpatients undergoing surgical consultation at major cancer centers meet the criteria for palliative care. In a study at MD Anderson of over 1000 inpatient surgical consultations, 40% met the criteria for surgical palliative evaluation [3]. The low overall median survival of all patients (2.9 months) highlights the need for a selective approach to patients undergoing palliative surgical consultation. Attempts to identify variables associated with poor survival, and perhaps identify

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patients that should be managed without surgery, were largely unsuccessful in this study although patients with two or more radiologic sites of disease and carcinomatosis had poorer survival. The risks of palliative surgery are significant as palliative surgical procedures have reported morbidity and mortality rates of 20–40% and 4–7%, respectively [3, 4]. In appropriately selected patients, palliative surgery can achieve up to 90% symptom resolution [4] and mean duration of symptom control of 135 days [5].

The most important factor in decision-making for surgical palliation is patient selection. While no single instrument has been defined as the best metric, several criteria have been proposed including symptom control, prognosis, preoperative performance, quality of life, tumor burden amenable to palliation, procedure-related morbidity and mortality, feasibility of nonsurgical options, anticipated duration of hospitalization, requirement for additional palliation, and cost [6]. Risk-benefit discussions during the consent process for palliative surgery are difficult owing to several limitations in existing data and research. First, the benefits of palliative surgery are largely unknown due to a paucity of high-quality, prospective, patient-reported outcome studies. Second, prognostication is difficult for advanced cancer patients, and the risks of surgery must be balanced against the estimated remaining length of life for patients undergoing palliative surgical consultation. There is no tool that specifically predicts complications for palliative intent surgical procedures. For example, the proportion of patients undergoing palliative surgical intervention for cancer within the American College of Surgeons National Surgical Quality Improvement (ACS-NSQIP) calculator pool is small, which limits the calculator's predictive ability for this population [7]. This calculator has been shown to significantly overestimate mortality but underestimate length of stay for palliative procedures [8]. Lastly, randomized clinical trials are difficult to perform in palliative populations and particularly in the palliative surgical population [9].

Despite a selective practice of surgical intervention, palliative surgery can still account for approximately 20% of a surgical oncologist's practice and over 1000 procedures per year at cancer centers [5, 10]. The frequency of palliative surgical consultation and intervention aids in the identification of common diagnoses and treatment patterns. Gastrointestinal obstruction is the most common indication for palliative surgical consultation at approximately 40% [3]. Gastrointestinal bleeding and wound complications/infections each account for 10% of palliative surgical consultations. Abdominal pain of unclear etiology is also common and often includes patients with constipation, ileus, carcinomatosis with resultant gastrointestinal dysfunction, and medication- or treatment-related side effects. The common theme throughout many of these palliative surgical consultations is the acute presentation of symptoms as these patients are often evaluated in the hospital or emergency department. Although acute in nature, palliative surgical consultations rarely require urgent surgical intervention and allow for time to engage in multidisciplinary care discussions and a thorough evaluation of the associated risks and benefits.

Gastrointestinal Obstruction

Gastrointestinal obstruction is one of the most common indications for surgical consultation, even in patients without cancer. The standard approach by general surgeons in the evaluation of patients with obstruction includes a history to identify the anatomic site and degree of obstruction. The approach to assessment of gastrointestinal obstruction proceeds similarly in patients with and without cancer. Past surgical history is an important component of the subjective assessment for patients with obstruction as adhesions and hernias are the two most common causes of obstruction. Cancer is notably the third most common cause in the bowel obstruction differential diagnosis in patients undergoing general surgery evaluation. The objective assessment should first focus on vital signs to evaluate for hemodynamic instability. Fever and tachycardia are findings worrisome for ischemia. A complete physical examination should be performed. A focused assessment of the abdomen is necessary to evaluate for strangulated incisional or inguinal hernias, the degree of abdominal distention, and peritoneal signs. Laboratory analysis is necessary to manage electrolyte abnormalities and evaluate for leukocytosis, which could also indicate ischemia. Imaging is frequently obtained, first with plain films, but computed tomography imaging is often required in cancer patients not only to determine the site of obstruction but also to evaluate for sites of metastases within the abdomen, multifocal obstruction, and ascites. Treatment should begin during the evaluation of patients with bowel obstruction and may include nasogastric tube decompression, intravenous fluid resuscitation, and Foley catheter placement.

There are various definitions for gastrointestinal obstruction in cancer patients. Definitions include malignant bowel obstruction, patients with bowel obstruction secondary to recurrent cancer, patients with stage IV cancer and obstruction, and definitions based on anatomic site of obstruction [11–13]. A definition formulated during an international multi-institutional and multidisciplinary conference tasked with creating a definition for subsequent palliative trials defined malignant bowel obstruction as (1) clinical evidence of a bowel obstruction via history, physical exam, or radiographic examination, (2) bowel obstruction beyond the ligament of Treitz, (3) intra-abdominal primary cancer with incurable disease, or (4) non-intra-abdominal primary cancer with clear intraperitoneal disease [14]. A simplified defini-

tion for malignant bowel obstruction is blockage of the small or large intestine in a patient with advanced cancer [15]. As treatment varies depending on the anatomic site of obstruction, defining the obstruction as gastric outlet, small bowel, or large bowel can help identify differences in the utilization of endoscopic or surgical procedures and also identify differences in outcomes such as survival or symptom improvement [9, 13]. Regardless of the definition, bowel obstruction in patients with advanced cancer is common with reported rates of up to 42% of patients with advanced ovarian cancer and up to 24% of patients with advanced colorectal cancer developing obstruction during their lifetime [16]. Adding to the complexity of defining bowel obstruction in cancer patients is that somewhere between 3% and 40% of obstructions may have a benign etiology and are caused by adhesions or strictures not associated with malignancy [17].

Emesis and abdominal distention in patients with incurable cancer can be due to a myriad of factors other than mechanical obstruction. Patients with advanced cancer can suffer from electrolyte abnormalities, cachexia with metabolic derangements, pain medication side effects, constipation, autonomic dysfunction due to plexus involvement from malignancies with a tendency for perineural invasion, and chemotherapy/radiotherapy side effects. There are many surgical consultations for bowel obstruction that are ultimately found to have gastroparesis, ileus, or constipation.

Bowel obstruction in patients with advanced cancer is rarely a surgical emergency and typically allows time to consider multidisciplinary aspects of the patient's condition. Previous treatment, cancer stage, and prognosis are unique variables to consider in cancer patients with gastrointestinal obstruction. Although accurate prognostication is difficult, it is helpful to attempt to determine if a patient can recover from abdominal surgery and obtain a meaningful quality of life prior to death from their malignancy. The next aspect of surgical decision-making to consider is morbidity and mortality rates, which are considerable in patients undergoing palliative surgery. Morbidity and mortality rates are widely variable in the literature with a range of morbidity from 9% to 90% and a range of mortality from 9% to 40% [16]. A recent series from our institution demonstrated morbidity and mortality rates for surgical intervention of 44% and 5%, respectively [13].

Recognizing the lack of randomized trials and limited data from observational and retrospective studies of patients with advanced malignancy and bowel obstruction, various groups have attempted to provide consensus statements and treatment algorithms for these difficult clinical scenarios. The working group of the European Association for Palliative Care has provided clinical practice recommendations that state surgery should not be routinely undertaken and will only benefit selected patients with end-stage cancer and mechanical obstruction [16]. The working group went on to recommend absolute contraindications to surgery, such as previous abdominal surgery that showed diffuse metastatic cancer, involvement of the proximal stomach, and ascites that recurs rapidly after drainage. Relative contraindications include poor general performance status, poor nutritional status, and extra-abdominal metastases producing symptoms that are difficult to control. Many investigators have sought to identify variables associated with adverse outcomes. A systematic review of surgery for malignant bowel obstruction reported that poor performance status, diffuse carcinomatosis, previous radiotherapy, and small bowel site of obstruction were associated with failure of surgery [18]. Additionally, ascites and carcinomatosis are frequently reported as independent indicators of poor survival and also diminished ability to tolerate oral intake after palliative surgical intervention [19–21]. The combination of ascites and carcinomatosis creates a situation that is rarely palliated with surgery, other than venting gastrostomy tube placement.

Gastric Outlet Obstruction

Gastric outlet obstruction is defined as obstruction of the distal stomach or proximal duodenum and is most often associated with gastric, duodenal, or pancreatic malignancy. Figure 59.1 demonstrates a CT image of a patient with gastric outlet obstruction secondary to gastric cancer involving the pylorus. Gastric outlet obstruction accounts for only approximately 20% of palliative surgical consultations for gastrointestinal obstruction but has a low median survival of 3 months, highlighting the need for selective surgical intervention [9]. Management options include surgical loop gastrojejunostomy or endoscopic stenting. As the majority of

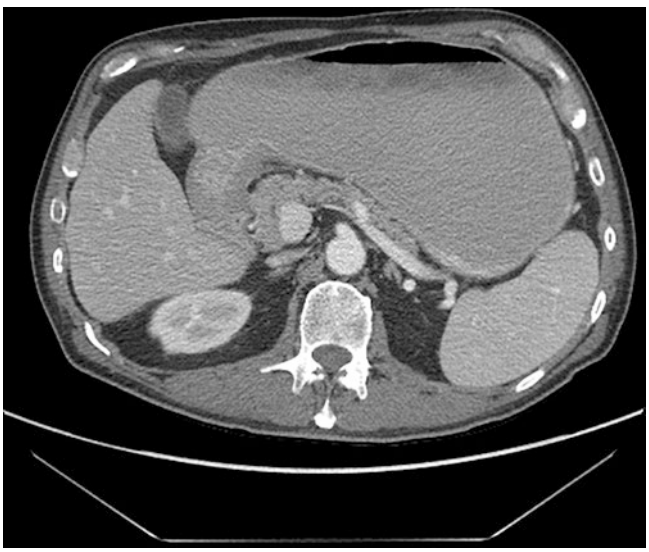

Fig. 59.1 CT image demonstrating gastric outlet obstruction

cancers that cause gastric outlet obstruction are associated with limited survival, prognostication plays an important role in treatment selection.

Although technically simple, morbidity and mortality rates after loop gastrojejunostomy are significant, and temporary delayed gastric emptying can occur [17]. Laparoscopic gastrojejunostomy may carry less morbidity and is associated with a lower incidence of delayed gastric emptying and faster resumption of oral intake [22]. Endoscopic stents, on the other hand, have less risk of morbidity and mortality but lack the durability of a surgical bypass [18, 19]. Stents can be complicated by occlusion or migration and are more likely to require re-intervention [23, 24]. A Cochrane review found that despite similar rates of technical success, stents were associated with a slightly shorter time to oral intake and a shorter length of stay [24]. This allows for earlier resumption of chemotherapy, although a survival difference has not been demonstrated [25]. Furthermore, stents are associated with a lower overall cost for index hospitalization and lower rates of 90-day readmission [23]. However, given the rates of recurrent obstructive symptoms and re-interventions in patients undergoing endoscopic stent placement, several authors have proposed surgery should be considered in patients with a life expectancy of 2 months or longer [21, 22]. A new technique for treatment of gastric outlet obstruction is endoscopic ultrasound-guided gastroenterostomy, which has shown similar technical and clinical success with less need for re-intervention impaired to endoscopic stenting [26], but long-term follow-up studies are needed [27].

Venting gastrostomy tubes are another option for patients with symptoms of nausea and emesis who have contraindications to surgical or endoscopic palliation. Gastrostomy tube placement may be performed through open surgery, laparoscopic surgery, endoscopy, or interventional radiology, although preference is given to the least invasive procedure possible as median post procedure survival rates are reported as only a few weeks [28–30]. Both endoscopic and interventional radiologic placement can be complicated by tube migration, leakage, and infections of the tube site, but literature reviews suggest endoscopic placement has fewer complications [24]. A retrospective review found that for patients who received a decompressing gastrostomy tube, a longer interval to placement was not associated with a change in overall survival, which suggests that venting gastrostomy tubes are often placed late in the course of disease [30].

Small Bowel Obstruction

Small bowel obstruction is defined as obstruction from the terminal portion of the duodenum to the ileocecal valve. Small bowel obstruction represents the most common indication for palliative surgical consultation in patients with gastrointestinal obstruction (64%) but has a similar median survival (3.5 months) to gastric outlet obstruction [13]. Only 25% of patients with small bowel obstruction undergo surgical intervention with the majority (52%) undergoing non-operative/nonprocedural management and 24% undergoing endoscopic/interventional procedures. The majority of endoscopic or interventional radiologic procedures in this population are venting gastrostomy tubes, as stents are typically not an option for small bowel obstructions. Many patients with advanced cancer and bowel obstruction have had previous surgery, adding difficulty in the differentiation of an obstruction due to malignancy from an obstruction due to benign adhesive disease. The surgical procedure is often not decided upon until completing exploration of the abdomen, and the two most common approaches are either bowel resection or intestinal bypass. A venting gastrostomy tube can be placed at surgery for patients with disease prohibiting resection or bypass, and conditions felt to be at high risk for early re-obstruction.

Large Bowel Obstruction

As many as 8–29% of patients with primary colorectal cancer present with malignant colonic obstruction [31]. Management options include surgical options of bypass, bowel resection or diverting ostomy placement, endoscopic stenting, or supportive care. Stents can be used as a palliative therapy in patients who are not good operative candidates or can be used as a bridge to surgery in patients presenting with an obstruction. A retrospective review found that stenting was clinically successful in 86% of patients undergoing palliative stenting and 89% of patients undergoing stenting as a bridge to surgery [32]. Stents are associated with a low risk of perforation [32] but can migrate or obstruct and thus require re-intervention [33] or urgent surgery in up to one third of patients [34]. Peritoneal carcinomatosis is associated with decreased technical and clinical success in stent placement [35], although a lower likelihood of delayed perforation [36]. The advantages of stent placement include shorter length of stay, avoidance of a stoma, and allowance for a better oncologic resection in patients who are later amenable to curative surgery [31, 33, 34]. Patients with inoperable malignant bowel obstruction can be treated with medical therapy including antiemetics, steroids, anti-secretory agents, octreotide, and hyoscine butylbromide [37]. One retrospective study found that 49% of these obstructions resolved with medical management, with functional mechanisms of obstruction more likely to resolve [37].

Gastrointestinal Bleeding

Similar to bowel obstruction, gastrointestinal bleeding in patients with cancer can be due to benign or malignant causes. The initial evaluation focuses on determining the severity of bleeding and assessing for hemodynamic instability. Utilizing the same initial approach taught through advanced trauma and life support training, surgeons assess the airway, breathing, and circulation of patients with gastrointestinal bleeding while ensuring adequate intravenous access. During this time, laboratory analysis should begin to include a complete blood count, blood typing and cross-matching, coagulation factors, and electrolytes with BUN and creatinine. A nasogastric tube and Foley catheter are often required for patients with active bleeding. Most patients are hemodynamically stable which allows time for medical management and diagnostic workup. Endoscopy is the primary modality utilized in gastrointestinal bleeding for diagnosis and therapy. Other less commonly required tests include tagged red blood cell scans, arteriography, and capsule endoscopy. As patients with advanced cancer are often best treated without surgical intervention, therapeutic options frequently involve embolization performed by interventional radiologists.

Bleeding secondary to tumor or treatment-related complications can involve many site-specific diagnostic and treatment issues. Tumors of the gastroesophageal junction and stomach often account for anemia through a slow rate of gastrointestinal hemorrhage and rarely require urgent surgery. In a recent review of 289 patients with advanced gastric cancer from Massachusetts General Hospital, only 3.5% required emergent surgery at presentation, of which none were performed for bleeding [38]. In addition, 233 patients in this series were managed without resection of the primary tumor, of which only 6 patients required subsequent emergency surgery for obstruction or perforation and no patient required surgery for bleeding. The low rate of surgical intervention for gastric hemorrhage is likely due to the many options available for bleeding secondary to tumor involvement such as endoscopic interventions, chemotherapy, and radiotherapy. For patients with gastric cancer, palliative radiotherapy can control bleeding in 70% of patients with a low rate of requirement for additional interventions during the patient's remaining life [39] and a duration of symptom control of 15 weeks [40].

Bleeding from small bowel tumors can be secondary to primary or metastatic malignancy. The small intestine can be a difficult diagnostic challenge as endoscopy will typically only assess to the level of the duodenum from above and terminal ileum from below. The remainder of the small bowel may involve arteriography or capsule endoscopy to accurately localize the site of bleeding. Bleeding from the large intestine and rectum can often be localized with colonoscopy, with the majority of cases attributable to primary colon and rectal cancer. Primary tumor response rates to palliative chemotherapy and radiation (for rectal cancer) are good and infrequently require emergent surgery.

Wound Problems and Infections

Palliative wound care can be a challenging clinical scenario that is of extreme importance to the patient. Problems related to wounds include bleeding, exudate, odor, pain, and limitations in function. Wound complications and infections are a frequent indication for palliative surgical consultation, representing 10% of palliative surgical inpatient consults at comprehensive cancer centers [3]. Treatment approaches include local wound care, excision, amputation, systemic therapy, and radiation. Traditional wound care management strategies are limited by the impaired healing of patients with advanced malignancy or patients that have received recent immunosuppressive therapy. Malignant fungating wounds are a unique challenge due to malodor and discharge that can affect up to 5% of people with cancer [41]. Figure 59.2 demonstrates a malignant fungating squamous cell cancer of the posterior scalp. Systematic reviews have identified few high-quality studies or effective therapies to guide the topical treatment of malodor and discharge in fungating wounds. However, a Cochrane review found one study showing that foam castings containing silver provided improved control of malodor, and another study showed similar results with regard to exudate, malodor, and pain with manuka honey and nanocrystalline silver dressings [42]. Although typically

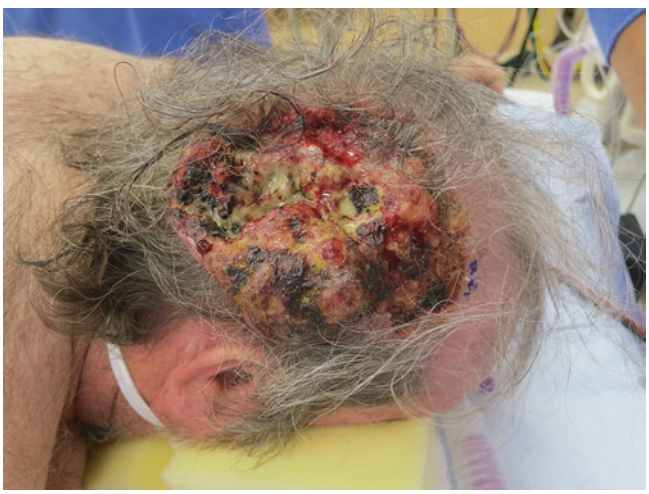

Fig. 59.2 Fungating malignant wound of the posterior scalp

used for more short-term wound care, one small study found that the use of negative pressure wound therapy for malignant wounds led to decreased pain, fewer dressing changes, and increased resumption of social interactions, with an average duration of 49 days [43]. Surgery is rarely an option but may be a last resort in patients that have wounds refractory to other therapy and are appropriate surgical candidates. Involvement of plastic surgery for advanced wound closure techniques is frequently required in patients undergoing surgery for wound problems.

Obstructive Jaundice

Options for treating biliary obstruction in patients with cancer include endoscopic stent placement, percutaneous catheter placement, or surgical bypass. Prognostication, although difficult and often inaccurate, can help identify the optimal treatment method. Endoscopic stent placement via endoscopic retrograde cholangiopancreatography (ERCP) is now the gold standard for biliary drainage as it is safe and effective [44]. Recurrent obstruction can occur but may be decreased with the use of self-expanding metallic stents. A systematic review and meta-analysis showed lower occlusion rates but increased rates of migration and pancreatitis for covered stents compared to uncovered stents, with no significant difference in survival or overall complication rates [45]. Percutaneous catheter placement by interventional radiology is often reserved for patients that fail endoscopic stent placement, as percutaneous procedures are more invasive. A systematic review and meta-analysis found that percutaneous transhepatic biliary drainage has a higher incidence of bleeding and dislocation but lower incidence of cholangitis and pancreatitis compared to endoscopic stenting. Yet, they found no difference in therapeutic success rate, overall complication rate, or 30-day mortality [46]. Endoscopic ultrasound-guided biliary drainage is a more recent procedure that can be used if ERCP stent placement is not feasible [47]. Several randomized controlled trials have found similar stent patency, adverse events, and re-interventions in centers where this technique is available [48].

Surgery is required in a fraction of patients but should be considered in patients that fail endoscopic attempts, live far away from referral centers with endoscopic expertise, or have other indications for surgical intervention such as concomitant gastric outlet obstruction. Even in the setting of gastric outlet obstruction, a gastric bypass and biliary stent may be preferred to a double bypass, as a double bypass procedure is associated with a higher rate of both biliary and non-biliary complications [49]. Figure 59.3 shows a CT image of a patient with concomitant bile duct obstruction and duodenal narrowing secondary to a locally invasive pancreatic neuroendocrine tumor. *Roux-en-Y* hepaticojejunostomy/choledochojejunostomy is the most frequently performed method of palliation and involves anastomosis of a 40–60 cm Roux limb to the bile duct in an end-to-side or side-to-side fashion. Anastomosis of the bowel to the gallbladder (cholecystojejunostomy) is a simpler method of biliary bypass that may be conducive to a laparoscopic approach, with acceptable results in small series [50]. However, a large population-based analysis of the SEER-Medicare data found a biliary intervention rate of 7.5% for patients undergoing cholecystojejunostomy and only 2.9% for patients undergoing bile duct bypass [51].

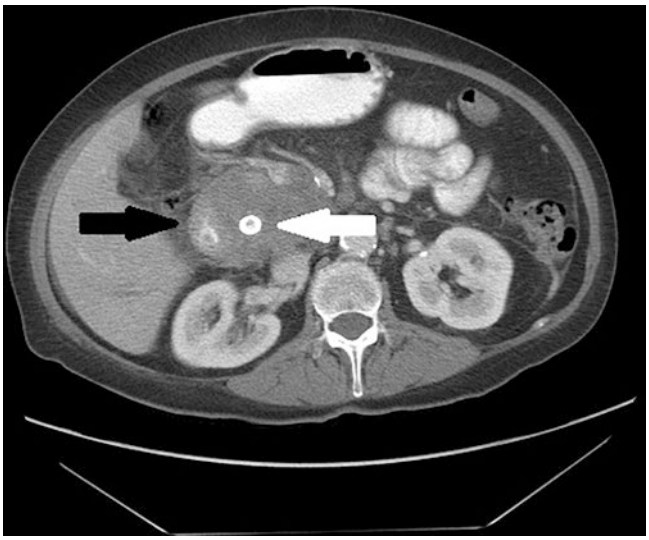

Fig. 59.3 CT image demonstrating a locally invasive pancreatic cancer causing narrowing of the duodenum (*black arrow*) and bile duct obstruction requiring metallic stent placement (*white arrow*)

Bowel Perforation

As with gastrointestinal bleeding and obstruction, there are benign and tumor-related causes of bowel perforation. Common benign causes of perforation include peptic ulcer disease and diverticulitis. Tumor-related causes include direct tumor invasion with perforation but also the side effects of cancer treatment such as immunosuppression, radiation effects, steroid administration, and the direct effects of chemotherapy that may render cancer patients more prone to bowel perforation. Cancer patients may also be more prone to iatrogenic bowel perforation due to the need for frequent endoscopic and interventional radiology procedures. As many cancer patients with bowel perforation have advanced or incurable disease, the optimal treatment is often based on a balance between the clinical presentation and oncologic prognosis. The majority of cancer patients with bowel perforation are treated with surgery with a 30-day mortality rate of 15% and morbidity rate of 46% [52].

Nonoperative care is another option, particularly in patients with incurable disease, and may have similar outcomes in select patients without abdominal tenderness, limited extent of perforation or contained free air, and aggressive treatment with antibiotics and drain placement [52]. One retrospective review found better outcomes after palliative surgery for intestinal perforation in patients who had higher albumin, low ECOG performance status, and absence of dyspnea and thus recommended consideration of nonoperative management for patients with unfavorable prognostic factors [53].

A unique and complex clinical situation is bowel perforation or fistula formation during treatment with bevacizumab. Bevacizumab is a humanized monoclonal antibody to vascular endothelial growth factor that has been proven efficacious in a number of disease sites, including several phase III randomized trials of patients with metastatic colon cancer [54]. Although generally well tolerated, bevacizumab has been associated with gastrointestinal perforation in 1–3.5% of patients [55, 56]. In a large retrospective review, risk factors for perforation included poorly differentiated signet ring cell carcinoma, stent use, and rectal location of primary and intact primary, although complications requiring surgery did not change survival [56]. Wound healing complications are increased in patients that undergo surgery during treatment, and most surgeons exercise caution in performing a gastrointestinal anastomosis in patients with bevacizumab-associated perforation [55].

Anorectal Infections

Anorectal infections and abscesses in noncancer patients are typically straightforward in management consisting of incision and drainage with complex treatment required in only a minority of patients. Anorectal infections in patients with immunosuppression, neutropenia, recent chemotherapy, or stem cell transplant and advanced hematologic disease can be a difficult palliative situation with considerable treatment and quality of life implications. Older reports of anorectal disease in neutropenic patients detailed associated mortality rates of up to 50%, while more recent reports suggest improvements in survival [57]. Anorectal infections in cancer patients are classified as either an abscess or perianal infectious process (pain or erythema without abscess/fluid). Necrotizing soft tissue infections are rare (~2%) but associated with significant mortality [57]. Patients often need imaging to evaluate for abscess or fluid formation, as physical exam findings can be misleading. Patients with fluid typically undergo an exam under anesthesia with drainage and seton placement or catheter placement via interventional radiology. Patients with a perianal infectious process without documentation of fluid are managed with antibiotics and close monitoring.

Ascites

Malignant ascites has a detrimental effect on quality of life with associated symptoms of abdominal pain, dyspnea, nausea, vomiting, anorexia, impaired movement, and fatigue [58, 59]. It is associated with limited survival, on the order of 1–6 months [58, 60–63], with only 11% of patients surviving greater than 6 months after the development of malignant ascites [64]. However, ovarian cancer has a more favorable prognosis than other primaries in the setting of ascites with reported survival rates of 24 months [64]. There are a wide variety of treatment options including diuretic administration, fluid restriction, systemic chemotherapy, intermittent paracentesis, peritoneal drainage catheters, and hyperthermic intraperitoneal chemotherapy.

Paracentesis is the most common treatment modality. In a physician practice survey, 98% of practitioners reported using paracentesis, and 89% reported it to be effective [65]. While paracentesis provides temporary relief for 90% of patients [66], repeat large-volume paracentesis is associated with decreased quality of life as paracentesis is only performed once symptoms recur [67]. Tunneled peritoneal catheters, such as the PleurX system, can provide a more durable option by allowing more frequent and smaller-volume drainage that can be performed outside of the hospital [68–71]. Tunneled catheters can be placed under fluoroscopic, ultrasound, or CT guidance and have reported technical success rates of close to a hundred percent in several retrospective and nonrandomized prospective studies [68–73]. The majority of patients with the PleurX catheter report good control of their symptoms, and the need for further interventions to restore catheter function is infrequent [71]. Surgeons infrequently perform peritoneal venous shunt placement due to its less effective control of ascites as well as higher complication rates, including sepsis, heart failure, disseminated intravascular coagulation, and shunt malfunction or infection [67].

Hyperthermic intraperitoneal chemotherapy (HIPEC) is combined with cytoreductive surgery in the treatment of peritoneal surface malignancy, appendiceal mucinous neoplasms, and colorectal/ovarian carcinomatosis. However, cytoreduction combined with HIPEC is a morbid procedure with an established mortality rate and lengthy post procedure hospitalization that is not generally appropriate for palliative surgical scenarios. Laparoscopic HIPEC, without cytoreduction, has been performed in patients with malignant ascites with excellent results in small series (Fig. 59.4). The laparoscopic approach appears to alleviate much of the morbidity – a multi-institutional analysis of 52 patients undergoing laparoscopic HIPEC reported a complication rate of only 6% with no postoperative mortalities [74]. Remarkably, the laparoscopic HIPEC procedure prevented re-accumulation of ascites in all but one patient [74]. Furthermore, small studies have found an average increase in Karnofsky performance scores of 20 points after treatment [74, 75].

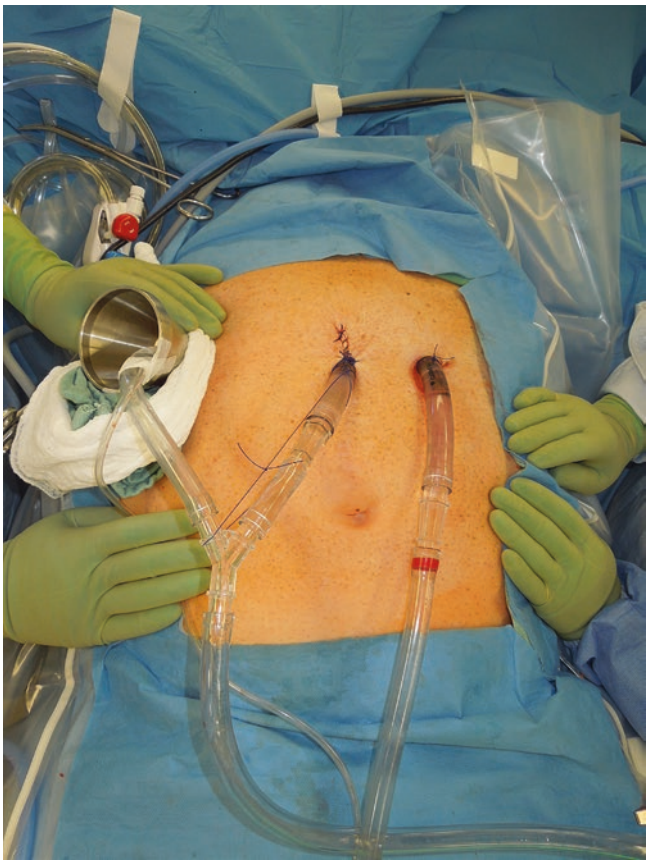

Fig. 59.4 Intraoperative cannula placement for laparoscopic hyperthermic intraperitoneal chemotherapy administration

Abdominal Pain in Unique Patient Populations

Celiac Plexus Involvement

Tumors with a propensity for perineural invasion, such as pancreatic cancer, can cause debilitating abdominal pain that radiates to the back. Pain in cancer patients, however, is infrequently attributable to a single cause but is more often a multi-factorial syndrome of tumor-related causes, treatment-related causes, and chronic pre-existing pain unrelated to cancer or its treatment. Opioids are the first line of treatment and often the only treatment that is needed. Palliative radiation is another treatment option for patients with pain secondary to celiac plexus involvement [76]. Celiac plexus neurolysis is a good local treatment option that can be performed through a percutaneous or endoscopic approach. Recent systematic reviews of plexus block procedures demonstrate improvements in pain with side effects usually limited to diarrhea, hypotension, and temporary increased levels of pain [77]. With multiple nonoperative options to alleviate celiac plexus-associated pain, surgical chemical blocks are relegated to the intraoperative scenario of finding unresectable disease during attempted pancreaticoduodenectomy. In such a situation, there is evidence from a randomized clinical trial that an intraoperative celiac block can lower pain in patients with preoperative pain and also prevent pain in patients without preoperative pain [78]. In situations where unresectable pancreatic cancer is detected during diagnostic laparoscopy, a laparoscopic celiac block has similarly been proven efficacious in reducing pain scores [79].

Neutropenia

Abdominal pain in neutropenic cancer patients presents a palliative clinical challenge as 90-day mortality rates are approximately 50%. The differential diagnosis includes causes of abdominal pain common in general surgery consultation such as bowel obstruction, diverticulitis, and appendicitis but also cancer treatment-related causes such as neutropenic enterocolitis and *Clostridium difficile* colitis [80]. Mortality associated with surgical intervention in the presence of neutropenia has been reported as high as 57% [81]. Surgeons will often deliberately delay treatment to allow for resolution of neutropenia, if possible [80].

Multiple Myeloma

Multiple myeloma is a plasma cell malignancy with systemic overproduction of antibodies resulting in bone pain, anemia, and renal insufficiency, with progressive tumor formation resulting in bone marrow failure. Surgical interventions are primarily palliative for long bone compression fractures or spinal cord compression. Abdominal pain requiring surgical consultation in myeloma patients is a serious condition with an associated 90-day mortality rate of 43% [82]. The differential diagnosis in this unique patient population is notable for the frequency of neutropenic enterocolitis (22%) and bowel perforation (13%) [82]. Prompt attention should be given to new complaints of abdominal pain in patients with myeloma as surgery may be required, although consideration should be given to the frequent comorbid conditions, severe sepsis, and recent administration of chemotherapy in the setting of a disease with often limited survival.

Outcome Measures

The palliative surgical literature is difficult to interpret due to the lack of commonly accepted outcome measures. In a review of studies from the palliative surgical literature, quality of life measurements were only included in 17% of stud-

ies, while morbidity and mortality were reported in 61% [83]. Morbidity and mortality, although important outcome measures in the risk analysis of surgery, must be balanced against patient-reported benefits of palliative surgery. Adding to the complexity of palliative surgical studies are the high attrition rate and difficulty in administering burdensome general quality of life instruments [84]. Observational outcome measures may provide some improvement in rates of postoperative symptom evaluation [85]. Future studies of easily administered, quick, patient-reported outcomes will be needed to identify the optimal outcome measure and then identify variables associated with outcome to select patients appropriately for surgery [86].

Conclusion

In summary, palliative surgical care is becoming increasingly recognized as critical in the multidisciplinary treatment of cancer patients. Traditional literature has focused on outcomes of morbidity and mortality with recent efforts to identify optimal patient-reported outcomes. There are few standardized guidelines for surgical intervention, and the decision to proceed with surgery is based on patient, family, and provider discussions incorporating a risk versus benefit model. Careful consideration is given to prognosis, although difficult and sometimes inaccurate, as well as future oncologic treatment options. As patients undergoing palliative surgical consultation are often dealing with severe symptoms, these discussions should be started as soon as possible, and attempts to anticipate future palliative clinical scenarios are helpful.

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Palliative Care

60

Sangeeta Lamba and Rebecca Goett

Integrating Emergency Palliative Care for Patients with Advanced Cancer

Seriously ill patients (with malignant and nonmalignant chronic illnesses) who suffer from a high disease and symptom burden often visit the emergency department (ED) for acute crisis events related to their illness [1–13]. Though the ED is primarily designed to resuscitate and stabilize the acutely ill and injured, increasingly those with chronic serious underlying disease processes such as malignancy seek care in this setting [1–5, 7, 10–18]. Malignancy-related symptoms and oncologic emergencies therefore often lead to ED visits, and these visits tend to increase as the patient's clinical status deteriorates and as they approach the end of life [1, 3, 4, 11]. Most hospitalizations in patients with underlying malignancy are initiated from the ED, and these early hours of care often include life-sustaining decisions such as ventilator support and symptom control that establishes, for better or for worse, the trajectory of future in-hospital care [15–20]. When a patient with a life-threatening oncologic emergency presents to the ED, these rapid decisions often occur in the context of uncertain prognosis and rapidly evolving clinical status, especially if the event was unexpected [17–20]. Determining goals of care rapidly so that initial treatment pathways align with patient values (thus avoiding future conflict) is challenging in most circumstances, but perhaps even more so in the ED setting [17–20]. At times, ED providers may need to change gears and shift their focus to comfort and quality of life goals for the patient (palliative care) as opposed to the traditional focus on cure or disease-centered treatment. Strategies to provide optimal care to the seriously ill patient with cancer include (1) use of best practice based clinical decision-making models [21, 22] and (2) incorporation of patients' values and goals in plans of care [15–19].

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The World Health Organization defines palliative care as an approach that "improves the quality of life of patients and their families when facing the problems associated with life-threatening illness, through the prevention and relief of suffering by early identification, impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [23]. Palliative care applies to *all phases* of a life-limiting condition and is not just for dying patients (Fig. 60.1) [11, 16, 17, 23–25]. In fact, maximal benefit is likely when there is early integration of palliative care into management plans as opposed to only considering such care as a last resort measure when "no more can be done" for the patient [1, 7, 16, 17, 23–31]. The early integration of palliative care is associated with a higher quality of life, including better understanding and communication, access to home care, emotional and spiritual support, well-being and dignity, care at time of death, and lighter symptom burden. In fact, some evidence suggests that, on average, palliative care and hospice patients may live longer than similarly ill patients who do not receive such care [6, 17, 32]. Palliative care also has the ability to simultaneously improve quality and control the cost of care for the most seriously ill patients [25, 28, 30–38].

The Institute of Medicine (IOM) report "Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life" highlights the current disconnect between how most Americans wish to be cared for at the end of their lives and the care that is actually pro-

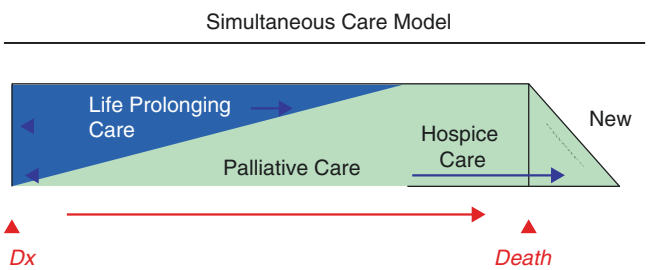

Fig. 60.1 Simultaneous care model of palliative care

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vided to them [32]. The report lists a similar disconnect between the services that seriously ill patients and families need and the services they currently receive [32]. People nearing the end of life often experience multiple transitions between healthcare settings (the ED being a major setting for end of life crises) and high rates of apparently preventable hospitalizations—which can further fragment the delivery of care and create an added burden for patients and families [32].

The IOM report also makes a recommendation that "All people with advanced serious illness should have access to skilled palliative care or, when appropriate, hospice care in all settings where they receive care (i.e., health care facilities including the ED, the home, and the community)" [32]. This report also proposes that comprehensive care for individuals with advanced serious illness who are nearing the end of life should:

- Be seamless, integrated, patient-centered, family- oriented, and consistently accessible
- Consider the physical, emotional, social, and spiritual needs of individuals and family
- Include coordinated, efficient information transfer across all providers and all settings
- Be consistent with individuals' values, goals, and informed preferences [32].

These proposed goals are consistent with palliative care principles and are integral components of both palliative care and hospice care (Table 60.1) [23, 26, 32]. However, it is important to note that hospice care services in the United States are primarily based on prognosis (as reimbursed by Medicare) and considered when a patient has a terminal prognosis with 6 months or less of predicted survival [16, 17, 20].

Palliative care is "whole person care" or patient-centered care and involves an interdisciplinary team, including board-certified or trained hospice and palliative medicine physicians, nurses, social workers, and chaplains, together with other healthcare professionals as needed [16, 17, 20]. Depending on local resources, access to this team may be on site, via virtual (phone) consultation, or by transfer to a setting with these resources and this expertise level, such as an in-hospital palliative care unit [16, 17, 20]. Although most now recognize the importance of the ED setting in caring for the seriously ill, many barriers and competing priorities for both ED and palliative care providers jeopardize more widespread integration of these two disciplines [16, 17, 39]. The term "integration" is used to indicate the incorporation of palliative care principles (outlined in Table 60.1) [23, 26, 32] into daily ED practice with or without the involvement of a dedicated palliative care team or inpatient palliative care unit.

Table 60.1 Principles and elements of palliative care[a]

Patient and family centered care Care plan is aligned with preferences and determined by goals of patient and family and there is a support system to help family cope with the patient's illness and with bereavement
Timing Support starts early in the course of illness and may exist along with therapies that are intended to prolong life (such as chemotherapy) Support continues until disease cure or patient death
Interdisciplinary team approach to care A team meets the needs of patients and families (may include nurses, social workers, clergy, nursing assistants, pharmacists, and volunteers)
Comprehensive care Multidimensional assessment to treat physical, psychological, social, and spiritual distress
Relief of suffering Prevent and relieve suffering from pain and other distressing symptoms
Skills in the care of the dying and bereaved Prognostication Offers a support system to help patients live as actively as possible until death
Quality of life Focus on enhanced quality of life (may also positively influence the course of illness) Regards dying as a normal process while affirms life
Continuity of care Ensure communication and coordination of care in transitions across settings Prevent crises and unnecessary transfers are important outcomes
Quality assessment and performance improvement[b] Address safety and incorporate the systems of care that reduce error Use validated instruments for data to measure outcomes, when feasible

[a]Patient population: patients of all ages experiencing a serious chronic or life-threatening illness or injury

[b]Crucial emergency department (ED) and hospital metrics may include ED visits, ED length of stay, time of arrival to time of disposition, hospital and intensive care unit (ICU) length of stay, hospital readmissions, ICU admissions, documenting advance directives, and pain/symptom control *Adapted from the National Consensus Project for Quality Palliative Care: Clinical Practice Guidelines for Quality Palliative Care and the World Health Organization palliative care Definition* [23, 26, 32]

Generalist Versus Specialist Emergency Palliative Care [17, 40, 41]

Many palliative care-related skills such as management of pain and other distressing symptoms as well as aligning management with a patient's goals of care are expected to be delivered by all emergency practitioners, so-called generalist practitioner level skills [7, 17, 22, 40, 41]. However, more complex palliative skills such as negotiating a difficult family meeting and managing advanced or refractory symptoms may require a "specialist level" of expertise [7, 17, 22, 40, 41]. Though it may be ideal to have a specialist manage all elements of palliative care, the reality is such that there are

Table 60.2 Generalist versus specialist levels of palliative care [40, 41]

Generalist-level palliative care	*Examples of tasks*
Provided by healthcare professionals who manage seriously ill patients, but palliative care is not the main focus of their daily work Includes care in settings not specialized in palliative care such as the emergency department	Basic management of pain and other distressing symptoms Basic discussions about prognosis, goals of treatment, and advance directives
Specialist-level palliative care	
Provided by healthcare professionals where main activity is the provision of palliative care Includes care in settings specialized in palliative care such as inpatient palliative care unit or hospice	Management of refractory pain or other difficult-to-treat complex symptoms Conflict resolution regarding goals of care (between family members and between family and healthcare team) Futility of care conversations

not enough specialists in the workforce, to do so. As people live longer with a higher burden of chronic illness, the demand for both generalist and specialist palliative care will rise [40]. Palliative care training programs have expanded nationwide, but the current levels of new trainees in palliative medicine will not meet the needs for all patients who may benefit from such "specialist" care [40, 42]. An optimal care model includes both generalist emergency palliative care (skills that all emergency clinicians should have) and specialist emergency palliative care (skills for managing more complex cases) (Table 60.2) [17, 40, 41]. The Education on Palliative and End-of-life Care (EPEC), EPEC-EM, and End-of-Life Nursing Education Consortium courses are examples of training that seek to build the generalist level of skills for emergency practitioners [43, 44]. Workshops and guides available from multiple resources also target further specific palliative skill development for interested practitioners [45, 46]. Due to the palliative care workforce gap, there is a growing need to develop generalist palliative care skills during emergency medicine resident training and also to provide continuing medical education to practicing clinicians [17, 40]. In addition, some state licensing boards require completion of pain and palliative care education credits prior to license renewal [47]. Performance and quality measure metrics can be used to reinforce the ongoing emphasis on generalist emergency palliative care as an integral component of high-quality patient care [27, 48].

Integrated Emergency Medicine-Palliative Care Initiatives

The Improving Palliative Care in EM (IPAL-EM) project is a resource development and dissemination initiative begun in 2010 by the Center to Advance Palliative Care (CAPC) with funding provided by the Olive Branch Foundation [7, 49, 50]. The goal of this initiative was to accelerate the integration of palliative care services into ED settings. It brought together an advisory panel of nationally recognized leaders in the disciplines of emergency medicine and palliative care [7, 22, 49, 50]. IPAL-EM offers an online portal for sharing essential expertise and available best evidence, tools, and practical resources to assist emergency clinicians and ED administrators in the successful integration of palliative care and EM [22, 49]. Currently, an institutional subscription to CAPC provides access to all the resources gathered as part of the IPAL-EM project, including clinical practice guidelines, needs assessment tools, and ED-specific quality metrics with a relevant library of peer-reviewed consensus/policy statements [49]. Finally, the American College of Emergency Physicians (ACEP) Palliative Care Section provides a variety of online resources to support ED-based palliative care [51].

Demonstration Models of Integrated Emergency Palliative Care

In the last decade, several programs have established ED palliative care initiatives to identify patients that may benefit from early palliative care interventions [22]. The IPAL-EM initiative collected information on existing models or demonstrations of ED and palliative care service integration. Eleven US hospital-based clinical integration programs were interviewed after they were identified from a review of literature, national presentations, and feedback from peer emergency palliative care experts [22]. These programs had varying levels of collaboration between their institutional palliative care program and the ED. Four themes emerged regarding ED palliative care programmatic development including (1) traditional consultation, (2) basic integration, (3) advanced integration, and (4) ED-focused advanced integration models (Fig. 60.2) [22].

Traditional Consultation Programs Similar to other consultation services that interact with the ED, a palliative care expert or consultant is contacted by the ED provider to help answer questions or issues in patient care and to help manage difficult-to-control symptoms [24, 40]. In this model there are no common programmatic goals or process steps to improve overall care delivery [22].

Basic Integration Programs In these models there exists a somewhat more formal relationship between the palliative care program and the ED, and they may work together to achieve some common programmatic goals and objectives. For example, there may be defined protocols for improved patient workflow such as expedited admission to a palliative care unit or targeted generalist-level palliative care education for the ED staff [22].

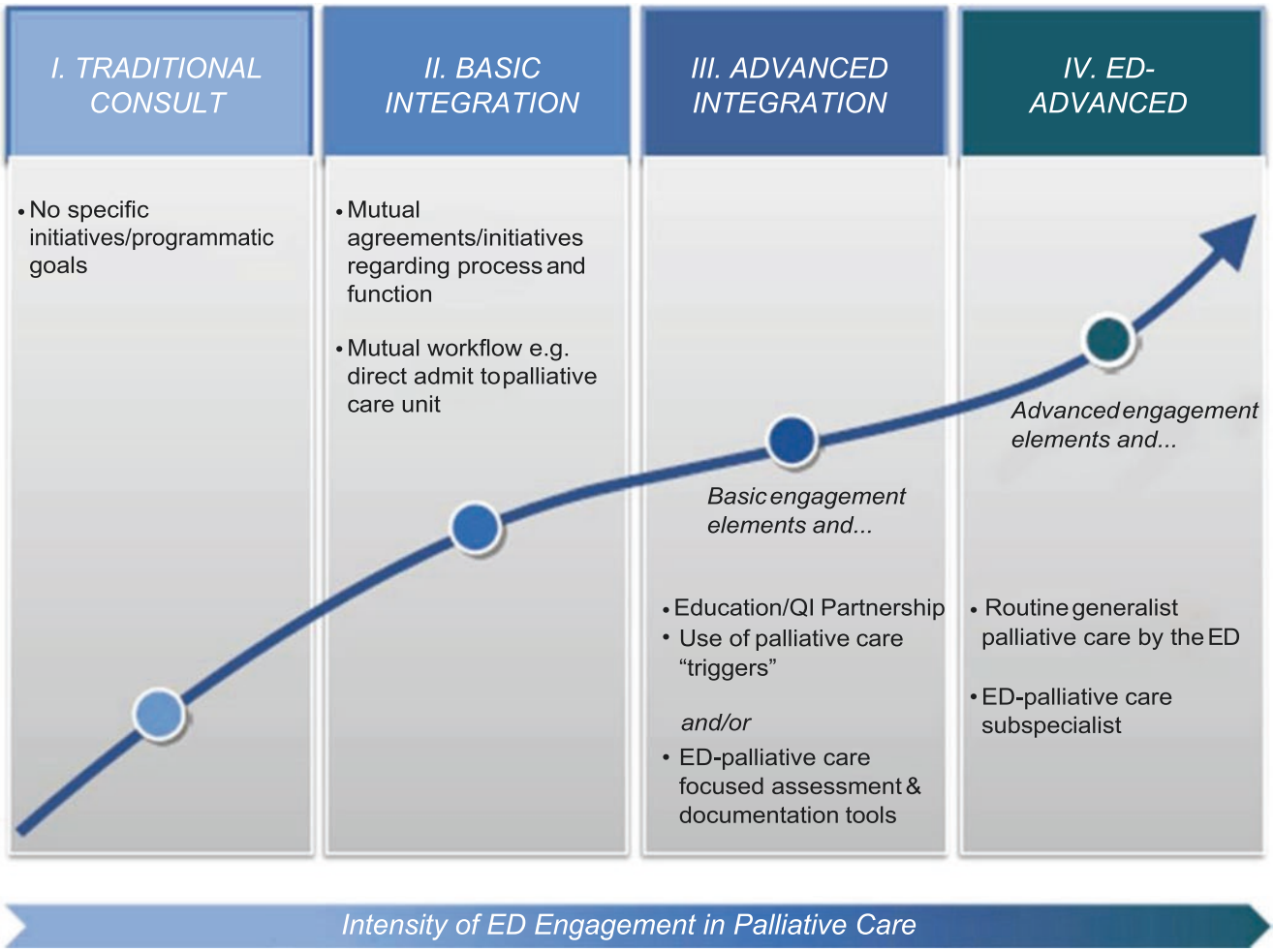

Fig. 60.2 Observed models of ED and palliative care integration [22]

Advanced Integration Programs These programs build on the basic integration models to set up common programmatic processes and protocols with the ED increasingly taking on a more active role, while an enhanced level of ED generalist-level palliative care is provided [22, 52].

ED-Focused Advanced Integration Programs In these programs, the ED is very engaged and focused on palliative care-related processes. In some cases the ED may lead the integration and the palliative care services in the institution. Common themes in these programs include case management for high-risk palliative care patients and existence of dual EM and palliative medicine-certified physicians who are passionate about the integration initiatives. Additionally, these programs often have increased numbers of personnel resources to support palliative care, including ED social workers or bereavement supporters for families. They may also implement reorganization and structural changes to improve patient care at the end of life, such as a designated private room or space for imminently dying patients and their families [22, 53].

Jump-Starting an ED Palliative Care Integration Initiative

Researchers have identified a number of important barriers to emergency medicine and palliative care integration. Surveys of physicians, nurses, and administrators list barriers such as (1) the ED culture of life-prolonging care and resuscitation that places a lower emphasis on nontechnical skills, (2) palliative care staffing and availability for the 24-hour, seven days a week, needs of the ED, (3) logistical issues including lack of access to patient medical records, and (4) medicolegal concerns particularly if life-prolonging therapy is not offered [10, 15, 39, 54]. One manuscript describes the ED as being "caught in the middle" when caring for such patients. It lists the challenging physical environment (privacy, noise, lack of information and delay, and lack of defined pathways), with limited resources (overcrowding, time pressures, competition with other emergencies) and variable roles and expectations of the staff providing care (comfort with dying, views of dying in the ED, expertise

and comfort in caring for those with serious and advanced illnesses) [10]. On the other hand, the emergency medicine resident and attending physician surveys report that they believe that palliative care skills are important for EM practice but that they are not yet adequately educated and trained in providing such care [15, 55]. Domains of particular interest identified for emergency physician training include management of patients under hospice care, withdrawal of life-prolonging measures, prognostication, and pain management [15, 17, 55]. Recently, hospice and palliative medicine educational milestones were developed for emergency medicine resident training [56].

It is important to begin an ED-PC initiative with identified ED "champions" who can effectively build upon lessons learned from other prior successes and failures so that the initiative is tailored to fit the unique ED setting [7, 50]. The design of the initiative should recognize the preexisting hospital and community resources, availability and hours of access to palliative care consultation services to the ED, and key institutional deficiencies in ED palliative care [7, 50]. Some common examples of initial targets for integration may include:

- Setting up an ED bereavement program
- Defining screening criteria to identify high-risk patients for early palliative care team interventions
- Educating ED staff on pain and palliative care protocols
- Embedding palliative care staff in ED rounds
- Improving throughput to the inpatient palliative care unit, when available

These initiatives have a higher chance of success if aligned with the key metrics important to the institution, such as ED length of stay, hospital readmission rates, and utilization metrics related to observation and intensive care units [7, 17, 48, 50]. Described below are four steps that may help jump-start such an integration initiative [7, 50].

1. *Put Together a Team: Palliative Care "Champions" in the ED*

Recruiting work group or team members who are interested and committed to the integration of palliative care in the ED is important. For example, identify those individuals who have previously expressed concern, frustration, or sensitivity to a patient's unmet palliative care needs. The interdisciplinary collaborative nature of palliative care allows for engagement of varied professional disciplines based in the ED such as social workers and case managers, as well as other providers throughout the institution who interact with the ED, such as chaplains. Since the integration initiative has the potential to impact other hospital services and processes, a wider range of administrative and clinical personnel should also be considered for inclusion. Table 60.3 lists some of the members to consider when setting up an initial work group. Though the type of members engaged in such an initiative will likely vary from one ED to another, it is vital to include key ED administrators such as the ED medical director and nurse manager(s) in the work group. They not only know their own ED's needs but can also provide valuable perspectives, taking into account resources (staffing, training needs) that may be critical for designing and implementing feasible integration efforts [7, 50]. The ED administrators may also be best equipped to engage support among both ED colleagues and at a broader institutional level.

Table 60.3 Suggested members for the emergency department (ED) palliative care integration initiative [7]

ED medical director
ED physician(s)
ED nurse manager and ED nurse(s)
Director or designee of the palliative care program
Nursing educator
Social workers
Case managers
Chaplain
Representatives of key hospital services (e.g., hospitalists, ICU, surgery, oncologic) that may be affected by this initiative in the ED
Hospital leadership: administration and finance
Others relevant to the success of a specific part of the initiative (e.g., ethics consultant, mental health professional, pharmacist)

2. *Explore the Resources Available: Existing Literature and Resources*

The literature in emergency palliative care is increasing rapidly. Consensus statements on the role of palliative care and ED such as the policy statements and the Choosing Wisely campaign from the American College of Emergency Physicians and Emergency Nurses Association on roles of the ED and ethical issues at end of life are important to note [57–59]. Specific guidance from the Choosing Wisely campaign states: "Don't delay engaging available palliative and hospice care services in the emergency department for patients likely to benefit" [57]. While there is no identified optimal model of ED integration of palliative care, there are a growing number of examples in the literature of specific strategies and programs that have proven to be successful [21, 22, 30, 31, 60]. Other topics relevant to emergency palliative care include:

- Palliative and end-of-life care in the ED [1, 2, 4, 5, 7, 16–20]
- Communication skills [5, 15]
- Family experience and surrogate decision-making [5]
- Palliative care specialists in the ED [19, 40]
- Ethical issues [5, 15]
- Quality improvement/practice change [48]

- Protocols and screening criteria [30, 31, 60]
- Family presence during resuscitation [17]
- Bereavement care [17, 25]
- Education and training [55, 61]

An open-access educational online resource published by the Palliative Care Network of Wisconsin, *Fast Facts and Concepts*, is worth noting since it provides concise, practical, peer-reviewed, and evidence-based summaries on key topics important to clinicians and trainees caring for patients facing life-limiting illnesses [62]. *Fast Facts* are free, easily accessible, and clinically relevant monographs on palliative care topics. They are intended as quick teaching tools for bedside rounds, as well as self-study material for trainees and clinicians who work with patients with life-limiting illnesses. For example, separate *Fast Fact* monographs review protocols for ventilator withdrawal protocol, guidance for calculating opioid dose conversions, and practical aspects of initiating a hospice referral from the ED [62, 63]. In addition, there are several formal educational opportunities in palliative care targeted to ED clinicians. Some programs address overall palliative care skills for many types of providers, while others target profession-specific skill development, for example, those for social work and chaplains. Sponsoring some or all of the identified "champions" at such a conference may help build an institutional pool of qualified candidates who can not only train others but could then be targeted for future career development. Some opportunities include:

(a) EPEC-EM (Education in Palliative and End-of-life Care for Emergency Medicine): EPEC-EM is a 2-day conference designed to teach clinical competencies in palliative care to ED healthcare professionals in a train-the-trainer format. The conference covers topics specific to ED practice including rapid palliative assessment, disease trajectories and prognosis, care of the hospice patient, chronic and malignant pain management, family-witnessed resuscitation, communication, and more. There is also a focus on techniques for teaching the curriculum to other emergency practitioners [43].
(b) ELNEC (End-of-Life Nursing Education Consortium): ELNEC offers a modular train-the-trainer end-of-life training program for nurses [44].
(c) Communication skills building workshops such as Vital Talk [45, 46] that have now developed ED-specific workshops.
(d) Hospice and palliative medicine fellowship.

The American Board of Emergency Medicine is one of ten sponsoring boards for the hospice and palliative medicine subspecialty. The ACGME provides a program listing and additional information about individual pro- grams that can be accessed online [64].

3. *Identify and Ease Access to Local Hospice and Palliative Care Resources*

Identify palliative care resources (both personnel and services) that are available: (1) within the ED, such as case managers; (2) in the institution, such as a chaplain, social worker, or bereavement counselor; and (3) in the community such as collaborative arrangements with hospice agencies [30, 31]. These resources are often available, but remain unfamiliar to the ED staff and even if known are not easily identifiable by ED staff at the time of critical need. Collating information and making it easy to access are therefore valuable. Other steps to ease access to palliative resources may include: (1) Identifying and listing various hospital and community resources (Table 60.4); (2) cataloguing their roles, responsibilities, and contact numbers; (3) posting call schedules for personnel in a visible, high traffic area of the ED for ease of access; and (4) identifying clearly the hours of availability of support personnel and whether they are available in person or by phone. Additionally, consider explaining roles and responsibilities of personnel. For example, social work and case managers may be essential partners when navigating disposition issues and maximizing community resource utilization [7].

Palliative Care Consults If the institution has a specialty-level palliative care team, it may be important to collaborate with them to create screening criteria that assist ED staff in identifying appropriate reasons for consultation (Table 60.5) [7, 60]. Since many such palliative care consultation teams offer in-person services during regular working weekday hours and phone support during off-hours and weekends, it may be useful to create collaborative guidelines to determine what will constitute a non-urgent versus urgent/emergent level of consultation [7, 40, 59].

Inpatient Palliative Care Units Similarly, if the institution has a specialized inpatient palliative care unit, it may be useful to not only establish formal guidelines and processes for admissions from the ED but also educate ED staff on the scope and capabilities of care in this setting. This collaboration

Table 60.4 Potential list of institutional and community resources [7, 50]

Palliative care team call schedules
Palliative care team hours of in-person availability
Outpatient palliative care clinic availability and practice hours
Community hospice: home and residential hospice
Chaplaincy support and availability
Social work support and availability
Bereavement support and availability
Ethics consultant
Child life specialist support and availability (for pediatric patients or children of adult patients)

Table 60.5 Screening criteria for a palliative care assessment at the time of admission [60]

A potentially life-limiting or life-threatening condition (such as malignancy)[a] *and*
Primary criteria:
Global indicators that represent the minimum that hospitals should use to screen patients at risk for unmet palliative care needs
The "surprise question": Would you be surprised if the patient died during this admission?
Frequent admissions (admissions for same condition within several months)
Difficult-to-control (moderate-severe) physical or psychological symptoms
Complex care requirements (functional dependency; home support for ventilator or tube feedings)
Decline in function or overall failure to thrive
Secondary criteria:
Specific indicators that may suggest a high likelihood of unmet palliative care needs
Admission from a long-term care facility
Metastatic or locally advanced incurable cancer
Chronic home oxygen use
Out-of-hospital cardiac arrest
Current or past hospice program enrollee
Limited social support (family stress, chronic mental illness, etc.)
No history of completing an advance care planning discussion/ document

[a]Life-limiting or life-threatening condition is defined as any disease known to be life-limiting (e.g., chronic obstructive pulmonary disease, metastatic cancer) or that has a high chance of leading to death (e.g., multi-organ failure, sepsis). Serious medical conditions for which recovery to baseline function is routine (e.g., community-acquired pneumonia in a healthy adult) are not included in definition

with the palliative team and ED may be able to prevent some unwanted ED visits, for example, by referrals to an outpatient palliative care clinic.

Hospice Collaborations In addition, appropriate referrals to hospice from the ED are feasible and may facilitate early dispositions [20, 63]. Since these decisions are based on patient-determined goals of care with engagement of loved ones, they have the potential to increase patient and family satisfaction with ED care [20]. Fostering collaborative relationships with local hospice agencies and engaging them in a timely manner for appropriate patients may help clinicians initiate hospice referrals directly from the ED [20]. These relationships also have the potential to improve dialogue when managing patients under hospice care who arrive to the ED with a crisis event related to control of distressing symptoms [20].

4. *Complete a Needs Assessment for ED Palliative Care*

An assessment of needs helps identify opportunities for improvement in ED palliative care. This may help with targeting of areas where simple interventions can lead to early success that in turn provides momentum to the integration initiative. The needs assessment can outline barriers to the integration initiative and specific institutional strengths and weaknesses and finally identify adherence gaps between best practice guidelines and local practice. This information can focus initial attention and aid decisions on assigning resources [7].

Table 60.6 Sample section of the needs assessment tool [26, 65]

Domain 2: Physical aspects of care				
Guideline 2.1: ED clinicians use a multidisciplinary approach to pain and symptom control				
Indicator		*Present*	*Absent*	*Comment*
2.1	ED clinicians collaborate with specialists from different disciplines to create a comprehensive pain/ symptom control plan of care	☐	☐	
Guideline 2.2: ED clinicians assess symptoms using validated assessment tools appropriate for patients across the life span				
Indicator		*Present*	*Absent*	*Comment*
2.2.1	Standardized pain assessment tools are used	☐	☐	
2.2.2	Standardized symptom distress assessment tools are used	☐	☐	
Guideline 2.3: Emergency nurses use nurse-initiated protocols to relieve the symptom burden of patients				
Indicator		*Present*	*Absent*	*Comment*
2.3	The ED uses nurse-initiated analgesic protocols	☐	☐	

Core guidelines for effective palliative care are outlined by the National Consensus Project for Quality Palliative Care (NCP) and address eight palliative care domains, including physical aspects of care and social aspects of care [26]. These guidelines represent goals and ideal practices that enable programs to define their own palliative program organization, resource requirements, and performance measures. These guidelines have been adapted to develop ED-specific clinical practice guidelines and translated into a "needs assessment tool" that programs may find useful to identify areas for improvement (Table 60.6) [65].

Monitoring Integrated Palliative Care Initiatives

The Agency for Healthcare Research and Quality (AHRQ)/ American College of Emergency Physicians conference on "Improving the Quality and Efficiency of Emergency Care Across the Continuum: A Systems Approach" identified four key topics or questions for emergency medicine and palliative care: (1) Which patients are in greatest need of palliative care services in the ED (identifying the target population in

Table 60.7 Potential measurable quality metrics and outcomes for an emergency department (ED) palliative care integration initiative

Operational
Mean/median ED length of stay (hours)
Discharge disposition status
ED arrival to time of disposition (to palliative care unit)
% With repeat ED visits within 30 days (within 60, 90 days)
% With repeat hospital admits within 30 days (within 60, 90 days)
Number of hospice referrals from the ED
Number of palliative care referrals from the ED (if available)
Clinical
% Charts with documentation of the healthcare decision-maker/ advance care directives
% Of patients prescribed opioids with bowel regimen on discharge
% Of patients with documented pain assessment on presentation and % reassessed
% Of families with documented offer of spiritual support after ED death
% Of patients in target populations who have a documented palliative care assessment
% Of caregivers in target patient populations screened for caregiver strain
Patient satisfaction
% Of ED patients who report being adequately informed about their condition or treatment plans and options
% Of families who report excellent overall end-of-life care after patient's ED death
% Of patients reporting satisfaction with communication regarding discharge instructions

need)? (2) What is the optimal role of emergency clinicians in caring for patients along a chronic trajectory of illness (what skills are necessary)? (3) What is the effect on healthcare utilization after the integration and initiation of palliative care training and services in the ED? and (4) What are the educational priorities for emergency clinicians in the domain of palliative care? The conference proposed that future emergency palliative care research gathers evidence in these domains using six categories of inquiry: descriptive; attitudinal; screening; outcomes; resource allocation; and education of clinicians [48, 66]. Examples of some relevant quality indicators to measure progress toward ED-palliative care integration are listed in Table 60.7. Emerging work is exploring the efficacy of decision support tools and accuracy of screening triggers and tracking outcomes of the initiatives described above [67, 68].

Health Economics

Building palliative care capacity or launching new integrated palliative care initiatives in the ED may have costs that can range from minimal to substantial. For example, if the goal is to identify patients with palliative care needs early in the ED, an approach that uses preexisting resources such as the ED triage nurse to screen will have nominal costs, whereas if a dedicated staff such as a social worker will perform initial screening, the cost will be substantial. Therefore, leveraging preexisting resources such as nurse and faculty educators for educational initiatives and sharing interdisciplinary team members such as social work across units may allow for significant success without a large financial impact. Use of qualitative assessment (QA) EMR consult triggers, documentation templates, or order sets are also relatively inexpensive to place but need promotion and education around implementation.

For major and advanced palliative care integration initiatives, the main cost is personnel related, and buy-in from the administration would be needed. Highlighting elements that are important to the institution such as the fact that palliative care has been shown to increase patient satisfaction, improve quality of life, and decrease number of ICU days (and therefore related costs) may be useful to make the case and the value proposition for funding palliative care [6, 17, 25, 28, 30–38]. Leveraging philanthropy may offer ways to get smaller seed funds to jump-start an initiative as well. Education of clinicians around existing re-imbursement pathways may also incentivize good practices. For example, in 2018, Centers for Medicare & Medicaid Services updated their policy for providers to code for reimbursement when they provide advanced care planning and goals of care discussions with patients.

Case Studies

Case 1 Communication Skills: Delivery of Difficult or Serious News

A 67-year-old woman with hypertension and a history of ovarian cancer with surgical resection 7 years ago presents to the ED with moderate shortness of breath. Since the patient is afebrile and has unexplained tachycardia, she has a CT scan of the chest performed to rule out a pulmonary embolism. Multiple large pulmonary nodules suspicious of metastatic disease are seen. This disease progression is new based on patient's records.

ED Tasks Communication of serious or difficult news, advance care planning, aligning goals of care, symptom control, psycho-social and emotional support, and disposition to hospital or palliative care unit.

Case 2: Rapid Goals of Care Discussion

A 68-year-old woman with diabetes and breast cancer with metastatic bone disease is undergoing palliative radiation for pain management. She has severe fatigue, fever, and short-

ness of breath with oxygen saturation of 87% on 15-liter non-rebreather mask and high flow nasal cannula. Her chest X-ray shows diffuse bilateral ground glass infiltrates consistent with coronavirus infectious disease 2019. She is awake, anxious, and struggling to speak more than two to three words. She wants her live-in boyfriend of 10 years to make decisions regarding intubation but does not want her only daughter engaged. She also says that if she stops breathing, "that's God's will."

ED Task Effective communication of serious news, rapid goals of care, identifying healthcare proxy, managing possible family conflict, ethical issues, symptom management.

Case 3: Symptom Management: Actively Dying Patient

Patient is an 83-year-old man with congestive heart failure NYHA Class 4 and prostate cancer with bony metastases and presents to the ED for acute respiratory failure and hypotension with septic shock. He is enrolled in hospice at home, but his wife got anxious because he was struggling to breathe and she says, "please help him." Patient has a do-not-resuscitate and do-not intubate order on file.

ED Tasks Symptom management, aligning goals of care, coordinating disposition, transitioning care to in-patient hospice and/or palliative care unit, bereavement, and spiritual and psychosocial support of caregiver.

Summary

Optimal care for the seriously ill patient with cancer in the emergency department includes an early integration of palliative care for eligible patients. This capacity for palliative care is built by fostering the skills and competencies for the generalist ED clinician who will provide much of this care to meet patient needs such as effective communication of serious news, aligning treatment with patient's goals of care and wishes, and managing distressing symptoms. Capacity is further built using an integrated approach with early identification of patients with complex palliative care needs who would benefit from specialist-level consultation in the ED and navigating patient and family to appropriate palliative care and hospice resources. Integration initiatives in the ED may have a higher chance of success when ED champions are fully engaged with palliative care experts to collaboratively define not only resources and processes but also appropriate metrics to track outcomes and measure impact of the integrated initiative.

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Hospice

61

Bonnie K. Marr and Danielle J. Doberman

Why This Chapter Is Important

Most emergency physicians can recall a patient presenting to the emergency department (ED) with severe pain, dyspnea, or other symptoms and having to give the gut-wrenching news of a new cancer diagnosis or significant disease progression [1, 2]. With sensitive discussion, the patient may reveal they were referred to hospice services by their outpatient specialist for management of their symptom burden or extensive disease progression and ultimately declined to follow these recommendations. Even more memorable is the patient who is currently receiving hospice services yet presents to the ED actively dying. These scenarios are common and stand out due to the complexity of untangling the patient and family's true goals when presenting to the ED. As a clinician new to a patient's journey with serious illness, negotiating the intricacies of "breaking bad news" or navigating goals of care—especially for a patient who may be actively dying—in a time-constrained environment with limited information available is unlike other areas of medicine. However, emergency providers are in a unique and important position to make an impact on the patient's overall illness trajectory and care plan. This chapter will provide additional tools for navigating these circumstances and highlight the progress that can be made despite the challenges of the ED.

Cancer continues to be the leading diagnosis for those enrolled in hospice according to the National Hospice and Palliative Care Organization, with 30.1% of hospice decedents having a principal diagnosis of cancer in 2017 [3]. Therefore, within this text, it is important to emphasize that emergency physicians should be facile in communicating the differences between hospice and non-hospice palliative care (PC), evaluating the reasons a patient may present to the ED while enrolled in hospice services, confirming patient and family goals of care, and utilizing available resources to insure a smooth transition across settings.

Background

The Center to Advance Palliative Care (CAPC) defines palliative care as "… specialized medical care for people with serious illnesses... Palliative care is appropriate at any age and at any stage in a serious illness and can be provided together with curative treatment" [4]. Serious illness may include diagnoses, such as cancer, cardiac disease, respiratory disease, kidney failure, dementia, HIV/AIDS, amyotrophic lateral sclerosis (ALS), and many other serious and progressive illnesses. CAPC emphasizes that palliative care should not be initiated based on a patient's prognosis alone, but rather on the need for specialized, coordinated medical care for patients living with any stage of a serious illness from diagnosis onward, and can be provided along with curative treatments. CAPC further defines the overall goals of palliative care to be improved quality of life for the patient and family through assisting with management of symptoms and enhanced coping, which often can include clarification of goals of care [4, 5].

Emergency physicians who engage in reviewing goals of care with a patient and/or family can find it challenging to describe hospice and compare and contrast its services to those offered by palliative care. Both fields share a common philosophy of care that prioritizes patient-centered goals, focuses on the patient and family adaptation to illness and coping, and offers proactive symptom management. Hospice, however, is a program of services for patients who have a prognosis of 6 months or less and is provided to those who forgo further curative or life-prolonging care to focus on dignity and comfort at the end of life [6].

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Under hospice care, a physician-signed "Certification of Terminal Illness" (CTI) is required, whereby that physician attests that the patient's prognosis is anticipated to be less than 6 months if the terminal illness were to continue on the anticipated trajectory. Emergency physicians may be asked to sign this form when making referrals to hospice from the ED. At the time of hospice enrollment, the patient designates their Medicare or other insurance benefits to hospice care rather than ongoing curative treatment for the terminal illness and/or related conditions [7]. A helpful resource to review when exploring hospice designation for providers and patients can be found at https://www.medicare.gov/coverage/hospice-care. In addition, the assessment may be complex in supporting the CTI, and your ED case manager or hospice medical director may have special expertise in reviewing this documentation.

When a Patient Enrolled in Hospice Presents to the Emergency Department

Patients presenting from a hospice model of care to the ED are often experiencing a crisis, such as uncontrolled or poorly controlled symptoms, new symptoms such as a seizure or bleeding, or caregiver exhaustion due to the demands of care for someone with a progressive disease [1, 8, 9]. Symptom control needs may simply outpace the capacity of the home environment. On arrival to the ED, patients and their family and support systems do not necessarily wish to revoke hospice. Rather, they seek the rapid assessment and provision of symptom control EDs are known to routinely offer. In the setting of duress, a loved one may call for emergency medical services because this is a familiar way to seek urgent medical care. This type of presentation represents a critical juncture to confirm goals of care and an opportunity to coordinate treatment with the hospice of the patient's choice and align care with the patient's wishes. Counseling the family regarding the patient's current clinical status or recent decline and evaluation for potential refractory symptoms is often required. In addition, as outlined in Table 61.1, coordination of care with the hospice of their choice to ensure needs are being met, expectations are managed, and clear communication provided may prevent hospital admission or a return to the ED.

Given the variety of life-prolonging treatments available in the ED setting, and procedures such as thoracentesis or addressing an unstable fracture, which can dramatically improve comfort for patients even in their last days, yet can carry iatrogenic risks, conversations to urgently confirm and clarify goals of care and discuss alternatives provided by the hospice should take place whenever possible before a plan of care is finalized. Patient-defined goals of care should dictate any testing and treatment and take precedence over ED protocols as these may no longer be appropriate in the context of the patient's wishes. The hospice where the patient is enrolled likely has information regarding advance directives, previous intended plan of care, and prior wishes of the patient. They may even be able to send personnel to the ED who can be helpful in further exploration of the patient's goals as well.

Table 61.1 Reasons hospice patients present to the emergency department [1, 9]

Patient and support system reasons	Hospice care coordination reasons
Symptom control not optimized and felt to be intolerable (e.g., pain regimen felt to be ineffective despite titration by hospice)	Inability to address patient needs in a timely manner to improve comfort/lessen suffering
Urgent new symptom (e.g., seizure, hemoptysis, urinary retention, impaction, epistaxis, fall with fracture, or need for suture/cast)	Poor communication and/or anticipatory guidance and education with the patient and family
Medical equipment or supportive device malfunction (e.g., gastrostomy tube dislodgement, oxygen supply running out)	Hospice arranged for ED presentation to assist with supportive device/medical equipment restoration in keeping with patient's advance directives
Patient and caregiver(s) have differing/conflicting philosophies of care	Equipment malfunction/failure without timely repair or replacement to maintain patient's comfort (e.g., nebulizer, suction device, home oxygen, BiPAP)
Caregiver fatigue or challenge meeting the demands of maintaining the patient's comfort/needs	Family new to hospice/hospice experience and unaware to telephone hospice for their needs
Conflict about life-prolonging treatments. These may be treatments that were discontinued (e.g., chemotherapy) or interventions that were never initiated (e.g., hemodialysis)	Patient traveling between hospice catchment areas with unanticipated symptoms and not sure how to obtain hospice assistance
Automatic response to patient distress, a loved one may call EMS because this is a familiar way to seek urgent medical care	Presenting from a skilled nursing facility where staff is to be directed by hospice team to provide care and staff unfamiliar with hospice procedures/policies without proper training and require urgent assistance
Patient has enrolled in hospice requesting full resuscitation and EMS activated in keeping with their advance directives	

Time for the Talk: Introducing Hospice

As outlined earlier in this chapter, patients presenting to the ED with an oncologic diagnosis may qualify for hospice services, including with discovery of disease progression or functional decline; however, clinicians may be hesitant to

broach the topic given the constraints of a time-limited interaction and perceived difficulty in coordinating this transition in care [10]. Emergency providers should feel empowered to assess a patient's hospice eligibility and review this with the patient's primary physician, often an oncologist, cardiologist, or other specialist. In introducing hospice, it is necessary to review a patient's understanding of their clinical situation, sometimes called their "prognostic understanding" [11]. Having a shared understanding of prognosis between all providers, patient, and family is key to a successful hospice referral. Next, a provider would review goals of care and ascertain if the patient's wishes are aligned with hospice philosophy of care. Many of the steps in determining the appropriate level of hospice care and reviewing what services can be provided through the hospice are nuanced and based on the patient's clinical status and wishes. Table 61.2 provides a quick reference for overview of the hospice referral process, and Table 61.3 reviews the levels of hospice care.

It is often helpful to include ED social work and case management as early as possible in the care of a patient for whom hospice is being entertained to help in exploring possible options. It may also be useful to discuss the patient directly with the medical director of the hospice of the patient's/family's choice for further coordination of care. While it may seem there are a lot of moving parts to coordinate transition to hospice from an ED visit, this may be an ideal opportunity to facilitate the patient's goals and help the patient and family negotiate a crossroads in their healthcare journey. When there is a pre-existing relationship with the local hospices within the hospital's catchment area and the ED and hospital, the process of direct admission into hospice care from the ED can work smoothly. In these circumstances, social work and case management teams likely have experience offering the patient and family choices of hospice vendors with varying capacities and then facilitating assessment by the hospice(s) of their choice. The ideal scenario is a transfer to either a hospice inpatient unit (IPU) directly from the ED or the arrangement of a hospice intake visit (initial visit by a nurse at the patient's home or place of residence who will admit the patient to hospice and review policies/procedures and medications for symptom control) on the same day as discharge from the ED.

However, despite these efforts, some patients and family may decline to enroll in hospice from the ED, preferring a discharge home without services. Hitting the proverbial pause button on a disease-modifying plan of care that may not be in alignment with the patient's values and wishes for the future they envision can be an important first step in developing a treatment plan which supports their wishes. Due to the time-compressed environment of the ED, connecting with the patient's primary care physician or primary physician of record (cardiologist, oncologist, etc.) to convey the need for further goals of care discussions and plan for further in-depth discussions in the outpatient setting can facilitate a smooth transition of care. The primary physician may wish to hold these discussions themselves or may request an outpatient palliative clinic consultation be arranged from the ED. If the patient/family are strongly considering hospice and have not yet confirmed this choice, another option is to arrange a hospice informational visit, during which a representative from the local hospice of the patient's choice visits the patient at bedside or in their home to explain the program and its services. This is an ideal opportunity to assist the patient and their family in the information-gathering stages.

Review of Emergency Department and Palliative Care Collaborations: Toward Developing Pathways for Efficient Transfer to Hospice Care

For ED patients who are eligible for hospice, collaboration between ED providers and the hospital's palliative care service may be useful to identify patients who would benefit from a palliative care consult, provide over-arching support for seeking out goal-concordant care, and assist with care coordination with local hospices as appropriate. Quest and colleagues developed the Improving Palliative Care in Emergency Medicine (IPAL-EM) curriculum and not only identified an algorithm for considering palliative care involvement but also review a stepwise process to promote emergency medicine and palliative care collaboration, including the use of a needs analysis [12, 13]. Each institution may differ in the results of the analysis, especially as the viewpoints of various stakeholders are considered; however, through CAPC, this tool kit is available to tailor collaboration based on the needs identified. In terms of hospice, there are opportunities to streamline communication between ED staff and local hospices as well as utilize the local strengths of the ED interdisciplinary team, including social work and case management, to make direct hospice referrals. Patients and families must have the freedom of choice regarding which hospice they choose, and staff should be educated to provide these options and assist with coordination of care. An ED with an established PC partnership may use standard mutually agreeable screening tools to identify patients with unmet palliative care needs for PC consultation and hospice eligibility. A number of screening tools exist to identify these patients [14–16].

Early PC involvement in the ED presents the possibility for increased efficiency in the form of decreased length of hospital stay, improved patient/family satisfaction, decreased ICU utilization, and increased direct hospice referrals [16–20]. Further, PC programs often have relationships with hospices within a hospital's catchment area and can build

Table 61.2 Coordinating transition to hospice from the emergency department [1]

Steps to consider	Why this is important	Potential resources to assist	Nota bene
Determine hospice eligibility	Patients must qualify for hospice based on general Medicare guidelines used in conjunction with disease-specific considerations	Remember "Certification of Terminal Illness" is required where the patient's prognosis is anticipated to be less than 6 months if the terminal illness were to continue on the anticipated trajectory with specific criteria required [6]. The criteria can be complex and generally provide evidence for the clinical judgment above with factors related to demonstrating overall decline in clinical status versus non-disease-specific and disease-specific guidelines. It is recommended to review if a patient is eligible for hospice with their provider of record and the hospice of choice [11]	Hospice and palliative care teams are great resources for information
Discuss with provider of record	Can confirm hospice eligibility, review remaining treatment options and current treatment regimen, coordinate care, and engage provider with trusted rapport with the patient	Oncologist or primary care doctor may be the point of contact. They also may wish to be the provider of record for the hospice	This provider may also want to speak to the patient/family directly, and therefore it is important to include this person in the beginning for care coordination
Elicit patient information preferences, understanding, and goals of care	Prior to introducing hospice, it is important to find out what information the patient and/or family wants to receive (e.g., some may not want to know specific prognosis), assess understanding of their status to better manage expectations and elucidate gaps in communication/knowledge, and *further establish specific patient-centered goals of care*	Please see earlier chapter on communication for specific strategies and resources	Consider palliative care consult
Review philosophy of hospice if compatible with goals of care	Review that hospice is not a specific "place," but a philosophy of care focused on comfort and dignity at the EOL. May be helpful to ask the patient's understanding of hospice or prior experiences to help directly address concerns	Helpful to have social work and case management involved in discussions and to assist in reviewing available care in the home if this is the patient's preference and clinically appropriate	Work with your department to have a ready list of local hospices for ease of providing written materials to patients/families
Hospice choices/facilitate coordination of care	SW/CM may be helpful in reviewing local hospice resources to provide patients and families with choices available. Once this is done, hospice liaisons may be involved to evaluate the case	It can be helpful to review the case with the medical director of the hospice of the patient's choice as hospices have varying policies/procedures regarding certain interventions, such as IVF, TPN, antibiotics, etc. This is also a chance to review level of care needs—patients must meet certain criteria to be admitted to inpatient units (IPUs)	May be helpful to have list of contact information for liaisons/medical directors for local hospices available for providers
Disposition preparation	What you will need to do: Generally, hospices will require a "Certification of Terminal Illness" and decisions regarding hospice provider of record (of note, this can be the hospice medical director). A finalized MOLST/POLST dependent on the state laws may be needed	What needs to be arranged with the hospice: Arrangement with the hospice for delivery of DME, hospice intake visit, and review of prescriptions that may be needed until a patient's enrollment in hospice is complete	Care coordination with the patient's primary provider, especially if transition to hospice is not possible at time of determination of disposition
Clear sign out!	All the time invested in discussions with the patient, family, hospice, and primary provider should be thoroughly discussed at sign out and carefully documented. Discussions and family meetings are important and like a procedure should be recorded	Given the intense nature of these discussions and the shift nature of most ED provider's schedules, consider introducing the new provider coming on shift to the patient and their family, if possible, to establish continuity and provide clear communication	As in any other discharge, a patient should be assessed for stability for transport and anticipatory guidance given to families as appropriate if there is concern for potential death during transport

Table 61.3 Descriptions and considerations for levels of hospice care

Level of care	Description	Considerations	Helpful facts
Routine	*Routine care* is hospice care that patients have caregivers who can provide around the clock care if needed, have stable symptoms or symptoms anticipated to be controlled utilizing measures accessible *within the home, or home-like settings*, such as an assisted living, group home, or long-term care environment [12]	Hospices can have different policies regarding caregiver availability (most—but not all—require someone available 24/7). Some may also allow a trial at home in the setting of a recent symptom exacerbation if the patient's primary wish is to be in the home, or a home-like setting, and there is a plan in place to address this symptom across care settings	Home hospice includes visits from the IDT and can include nurses, social workers, chaplains, home health aide, and trained volunteers, with the physician of record overseeing care
Continuous	*Continuous care* can be provided in times of crisis (must be 8 out of 24 h), and 50% of this time must be provided by a nurse [12]	It is important to discuss with the hospice if a patient transferring from an acute care setting into continuous care may be better served by GIP level of care	It is helpful to review with the hospice of their choice what their policies are surrounding providing continuous care
General inpatient (GIP)	*GIP* level of care typically requires pain or symptom management in an inpatient facility that cannot be provided in another setting [12, 13]	Hospices will evaluate the symptom burden being considered, what has been done to address it, and potential for future exacerbations and complications	Generally, this is not meant to be the final disposition for the patient as they will be transferred to a less intense level of care once symptoms are stabilized. However, the facility may allow the patient to remain if death is considered imminent
Respite	*Respite care* is meant to provide temporary relief of caregiver responsibilities and has specific parameters surrounding this benefit [12]	Consider respite care for patients whose caregivers require a temporary "respite" from caregiving responsibilities, or if there are temporary reasons why the patient cannot stay in a particular routine LOC setting, but otherwise does not qualify for GIP level of care and is considered routine. Examples include the caregiver themselves falls ill, or a protracted power outage in the home of an oxygen-dependent patient makes return for a few days impossible	Collaboration with social work and other members of the ED IDT may be helpful. Remember: patients may present from hospice to the ED with goals of care unchanged related to social reasons and respite care may provide a solution

working relationships for protocols between the hospital and the hospice of a patient's choice when the need for hospice is identified by an emergency provider, and communication is required to jump-start the transition from the ED to hospice placement. In these cases, a PC consult may not always be required, but through a pre-existing collaboration, the process can be developed to make a referral seamless and routine, rather than requiring admission for disposition determination, especially if not desired by the patient and family.

Case Studies

Case Study 1

Mr. M is a 73-year-old man with past medical history significant for hypertension, coronary artery disease, and stage IV non-small cell lung cancer (NSLC) diagnosed 7 months ago and known metastases to the bone and liver. He has recently developed recurrent malignant pleural effusions, and due to his worsening dyspnea, pleurodesis has been discussed versus *a tunneled indwelling pigtail drainage catheter. He presents to the ED today complaining of profound dyspnea, especially with mild exertion such as trying to cross a room from bedroom to bathroom, and he had a small amount of hemoptysis earlier, of about a teaspoon in volume, 4 or 5 times. His last available documentation in your healthcare system's medical record reveals initial discussions were held about hospice with decision to maintain code status as a "full code." He had been awaiting review of potential clinical trials at a nearby academic center before electing to enroll in hospice care. You note that he has been to the ED once already this month and received an emergent thoracentesis and was evaluated by radiation oncologic without plans for further radiation at this time. He also describes worsening tolerance to activities of daily living (ADLs), requiring his wife's help to bathe and dress, and that he is spending more than half the day laying down or sitting in a chair.*

Question: Does Mr. M Meet Criteria for Hospice Enrollment?

Gather Information Patients may be referred for hospice services if their illness physiologically meets criteria of a prognosis of 6 months of less, should the illness run its usual course, and, after counseling regarding the implications of this prognosis and available options, have accepted this prognosis and elect a treatment regimen and plan of care which focuses only on comfort-based treatments and services. In this case, documentation by the oncologist supports the introduction of hospice due to the extent of progression of Mr. M's NSLC and specifically mentions that no further disease-modifying treatments are available outside of a clinical trial.

In addition, his worsening performance status also supports this assessment. The use of the Palliative Performance Scale (PPS) may support the evaluation as well. A recent systematic review by Baik et al. *assessed the capacity for the PPS—a prognostic index independent of a specific disease, which is based on functional status variables—to estimate survival at the end of life found: "All nine studies reported a significant association between PPS scores and survival among palliative care patients with advanced cancer"* [21].

Pause and Consider: How Would You Explore Goals of Care with Mr. M?

Gather Information If needed, consider accessing free resources to guide goals of care discussions, including those available through VitalTalk.org and resources from CAPC (if available at your institution).

Back to the Case Mr. M tells you he has been giving thought to hospice and asks if he will "go there to die." You review that hospice is a Medicare benefit based upon a philosophy of care rather than being in a specific place and that care and services can be provided in many settings, including the patient's home. You review that benefits include careful attention to symptom management with the ideals of maintaining comfort and dignity at the end of life. You also mention that the patient can choose to leave hospice at any time and re-enter hospice care at a later date [5, 10]. *He states he is tired of repeated visits to the hospital and worries about the stress on his wife. He also notes the clinical trial "doesn't seem like it would help me much anyway." You provide reflective listening and inquire how best to preserve his quality of life for as long as possible. He identifies goals of maintaining independence and being home with family. You echo how his goals can be incorporated into the plan of care and review how hospice can insure these remain cornerstones of his care plan. He and his wife agree with referral to social work and case management to evaluate which hospice would best meet their needs and arrange next steps. You also offer to call his oncologist and provide the update about the hospice referral, and he appreciates this coordination.*

Pause and Consider: What Further Information Would Be Helpful to Know for His Disposition and Management?

Gather Information Please reference Tables 61.2 and 61.3 *for guidance on what information would be helpful in assessing hospice level of care (LOC) and arranging the enrollment process. A detailed outline of this process is also presented in the article by Drs. Quest and Lamba: Hospice Care and the Emergency Department: Rules, Regulations, and Referrals* [1].

Additional Interventions During your phone call with the oncologist, they agree with the hospice plan and elect to be the physician of record for Mr. M's hospice care. You share this news with Mr. M who is appreciative of this continuity of care and notes he has provided the choice of hospice to the social worker on the case. After making the referral, the social worker asks you to report the symptoms Mr. M is experiencing and his current management for the hospice to review. After reviewing his vital signs, you note that he is mildly hypoxic at 93% on RA at time of arrival and has improved to 97–100% on oxygen via *nasal cannula. He is otherwise hemodynamically stable, and his chest X-ray reveals adequate placement of the pigtail catheter; however he has had worsening evidence of possible lymphangitic spread from imaging done on his last visit to the ED and continues to complain of significant subjective dyspnea, despite improvement in his oxygen saturations. Based on his volume status (which you assess as likely hypovolemic), you opt to avoid diuresis at this time and instead implement low-dose oral morphine, as opioids can alleviate the sensation of subjective dyspnea* [22]. *Mr. M does not identify symptoms aside from dyspnea and reviews his priority of returning home again on reassessment. You broach code status with him, and after careful counseling, he elects to remain full code as he is looking forward to seeing his grandson graduate from college in 2 weeks and demonstrates in his responses that his code status is emotionally tied to this milestone event.*

Consider: What Might Be Important to Sign Out to the Hospice of His Choice?

Gather Information Review what you would typically sign out for ongoing care for a patient, and consider how this care should be transitioned across settings.

In your review of his overall clinical status, including hemodynamic stability and improvements in subjective dyspnea with low-dose opioids, your assessment concludes that his comfort can be maintained at home with routine hospice care as his symptoms likely do not require rapid medication titration. If Mr. M did require more aggressive control of his symptoms, and more frequent reassessment and titration, these could be available in an IPU or via *short-term, continuous care services in the community. Returning to his own home is consistent with his goals of care, and social work reveals that he has 24/7 caretaker support in the home. Further, the hospice is able to arrange for a nurse liaison who can do an intake visit tonight, with DME equipment delivery tomorrow morning, which is acceptable to the patient. You confirm this with the hospice, review his decision to remain full code at this time, and also discuss that he has a pigtail catheter that he has previously been given education on utilizing and that he will require ongoing nursing care to maintain. You also request oxygen for symptomatic control of dyspnea, with the standard hospice parameters of "titrate for comfort." After summarizing his case, the hospice provides instruction and requests prescriptions for medications to address symptoms that may evolve in the coming days.*

Case Study 2

Ms. H is a 90-year-old woman with history of Alzheimer's dementia presenting from home hospice to the ED via *EMS. Her vital signs are unremarkable, and her daughter reports that she is concerned hospice is not providing the care that her mom requires. After further discussion, you learn the patient's daughter was recently diagnosed with breast cancer and requires surgical intervention with a lumpectomy and lacks other social supports to continue caring for her mother at home. The patient's physical exam is benign overall, and the daughter denies changes in behavior or new symptoms. Your exam is consistent with an alert, non-verbal patient who does not follow commands or provide responses to questions but does not appear to be in any acute distress. You do not observe signs of neglect. Your colleague inquires if you're planning to admit the patient given limited resources at home for social reasons?*

Question: What Next Steps Should Be Considered?

Gather Information

- *Confirm goals of care based on substituted judgment.*
- *Evaluate the family's concerns and underlying reasons for presentation.*
- *Consider how collaboration with the patient's hospice can be utilized.*

You call the patient's hospice and learn that the hospice interdisciplinary team (IDT) was unaware of the daughter's diagnosis and impending surgery. They report the patient has only been on service for 5 weeks, and the IDT has found the daughter to be very private about sharing personal information and is unmarried with no children to offer additional support. In addition, the IDT shares that she has appeared reluctant to accept assistance at times, including declining the use of care aides and volunteers. After learning this information, the hospice offers to send a social worker to the ED to discuss care plan options and goals of care directly with the daughter. Via *the social worker, the hospice offers to provide 5 days of respite care at a local skilled nursing facility, and after further discussion with the patient's daughter, she agrees to this plan and is appreciative. The hospice social worker also shares with you that the daughter is the youngest of the patient's five children and the only daughter. She has voiced her fear that her brothers (all out of state) will feel she is not taking "good enough care of mom" if she allows others to help or to allow a respite. The social worker and the patient's daughter telephoned two siblings from the ED who both confirm that all the siblings consider the daughter to be the spokesperson for the family with plans to inform the remaining brothers of the plan. They provide reassurance to the patient's daughter and endorsed the need for the daughter to take care of herself and for the respite to proceed.*

This case underlines the importance of collaboration with the hospice agency when a patient presents to the ED while enrolled in hospice services. It is necessary to have careful discussions with the patient's surrogate decision-maker for healthcare to uncover the reason behind the presentation and confirm goals of care. At times, addressing communication challenges between the patient-family unit and the hospice is essential to providing the care the patient needs and can avoid unnecessary admissions.

Case Study 3

Mr. R is a 68-year-old man with history of COPD on 2L of oxygen via *nasal cannula at home and long-term steroid*

dependency. He presents with a femoral neck fracture acutely after tripping over his oxygen tubing. After initial stabilization and consult to orthopedics, you note that he has recently had repeated exacerbations requiring frequent hospitalization (three times in the last 2 months) and his FEV1 is less than 35% of predicted with weight loss of over 15% in the last year as noted by his pulmonologist. He also has had worsening functional status with recent need for a move to an assisted living facility. His daughter is a physician and advocated for him to be a lung transplant candidate recently with reported decision that he was not a candidate at a major academic center during the last month. He also has not regained function with pulmonary rehab and has been determined to not be a candidate for surgical intervention. In essence, his pulmonology records indicate that they are hoping to achieve stability with his new, worsened, clinical status. You assess that he is demoralized and asks you if there is an alternative to returning repeatedly to the hospital?

Pause and Consider: What Factors About His Presentation Make Him a Candidate for Hospice? If He Elects Hospice, Is He Ineligible for Operative Management of His Fracture?

Assume the Following Has Been Pursued

- *You consult to hospitalist service, and they plan to admit him and further review his pre-operative risk.*
- *A femoral nerve block significantly improves his pain.*

Gather Information You confirm that his FEV1, ongoing oxygen requirements, repeated admission, and need for ongoing steroids and other pulmonary treatments are considered indicative of a more guarded prognosis [23]. *Furthermore, his lack of other options to manage his disease state further supports a hospice admission.*

Patients can revoke hospice due to both changing their mind about goals of care (including when a new treatment becomes available) and be admitted for procedures that are considered to have greater benefit than burden for their quality of life based on their goals of care [12]. *An unstable femoral neck fracture in an ambulatory patient with a prognosis of months to years is likely to have significant impact on Mr. R's quality of life, and operative intervention (if he is considered a candidate) may allow him to have greater mobility and less pain over the time that he has remaining. In addition, COPD is historically difficult to prognosticate, and the factors mentioned above generally have been used to assess prognosis in terms of years rather than months* [23].

Consider palliative medicine consultation in addition to assessment of pre-operative risk and orthopedics consultation to help review possible treatment options, confirm goals of care, and promote shared decision-making.

Conclusion

Hospice offers an important resource for patients reaching the end of their lives and their families. Emergency physicians should be skilled at identifying patients eligible for hospice services and addressing this topic as part of a goals of care discussion, as well as assessing the unmet needs of hospice patients who present to the ED from a setting where hospice care is being delivered [24, 25]. Cancer represents a disease where hospice may eventually become appropriate based on the patient's goals and overall clinical status. Therefore, just as it is necessary to recognize common oncologic emergencies in order to provide excellent care, recognizing hospice eligibility, exploring reasons for presentation from hospice settings, confirming goals of care, utilizing resources within ED IDT and PC teams, and collaborating with hospice teams in providing care across settings are all important skills for the emergency provider to have at the ready for this patient population with complex care needs. This chapter has sought to review the basic steps in this process and underlines how the ED is a critical setting for assessing the needs of patients at pivotal points in their disease trajectory and offers an important opportunity to insure the delivery of ongoing goal-concordant care.

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Communication

62

Bonnie K. Marr, Kate Aberger, and Rebecca Goett

Introduction

This chapter will focus on how we communicate with the oncologic patient and their families in the emergency department (ED). Clinicians will learn how to facilitate discussion of emotionally charged topics with patients in a compassionate, effective, and timely way.

It can be argued that communication is as important as the technical aspects of treating disease [1–5]. Patients are suffering and they come to us for help. As physicians, we seek to understand the person with the disease and their wishes for the management of what ails them [6–8]. We can learn to harness our empathy – detecting another's emotions and experiencing their feelings of suffering – and learn to respond to this suffering with compassion. This type of communication can have positive measurable outcomes, for both the patients and us [9–13].

The main skill that palliative physicians practice frequently is a *goals of care* conversation. Although lengthy care discussions may seem impractical in the ED, there are methods to help acute care providers engage patients in these difficult conversations in brief but effective ways. We will use cases to illustrate "abbreviated goals of care conversations" [14] and give the reader some concrete examples of techniques to incorporate into everyday practice.

Components of an initial assessment by the emergency physician not only are vital to the provider determining a differential diagnosis and treatment plan but are also essential elements to consider in reviewing options with the patient and family in shared decision-making. As we are doing our initial resuscitation, we ask ourselves: Is this a reversible process? Is this a treatable process (but one that will not reverse the underlying disease), or is this patient actively dying [15]? Having transparent dialogue with a patient or family and building a shared plan for ongoing management help ensure clear communication about what next steps and expected outcomes may be in order to help patients and families feel prepared. Frequently the emergency physician has mere minutes to build rapport with a patient and gather information about his/her preferences for care. How do we identify those in need of deeper conversations? How do we recognize patients with unmet palliative care/communication needs? General guidance exists for emergency providers regarding when palliative care consultation and interventions should be considered. George et al. has developed a screening tool (Fig. 62.1), and the Centers to Advance Palliative Care has an initiative called "Improving Palliative Care in Emergency Medicine" or IPAL-EM, which also offers a screening tool [16–18].

Prognosis

In order to recognize a worsening prognosis, we must first look at the trajectory of the patient's illness (Fig. 62.2) [19].

Prognosis is generally based on two variables: (1) disease state and (2) functional status. In the oncologic patient, there are a few guidelines that we can follow. As shown above, terminal illnesses such as cancer usually preserve functional status until near the end. Then a precipitous acceleration of illness occurs once functional status begins to decline. Therefore, functional status is key to prognosticating in cancer patients. The median survival times for multiple brain metastasis, malignant hypercalcemia, malignant pericardial or pleural effusion, carcinomatous meningitis, malignant ascites, and malignant bowel obstruction are relatively short (weeks to months) and can be estimated with some degree of accuracy [15].

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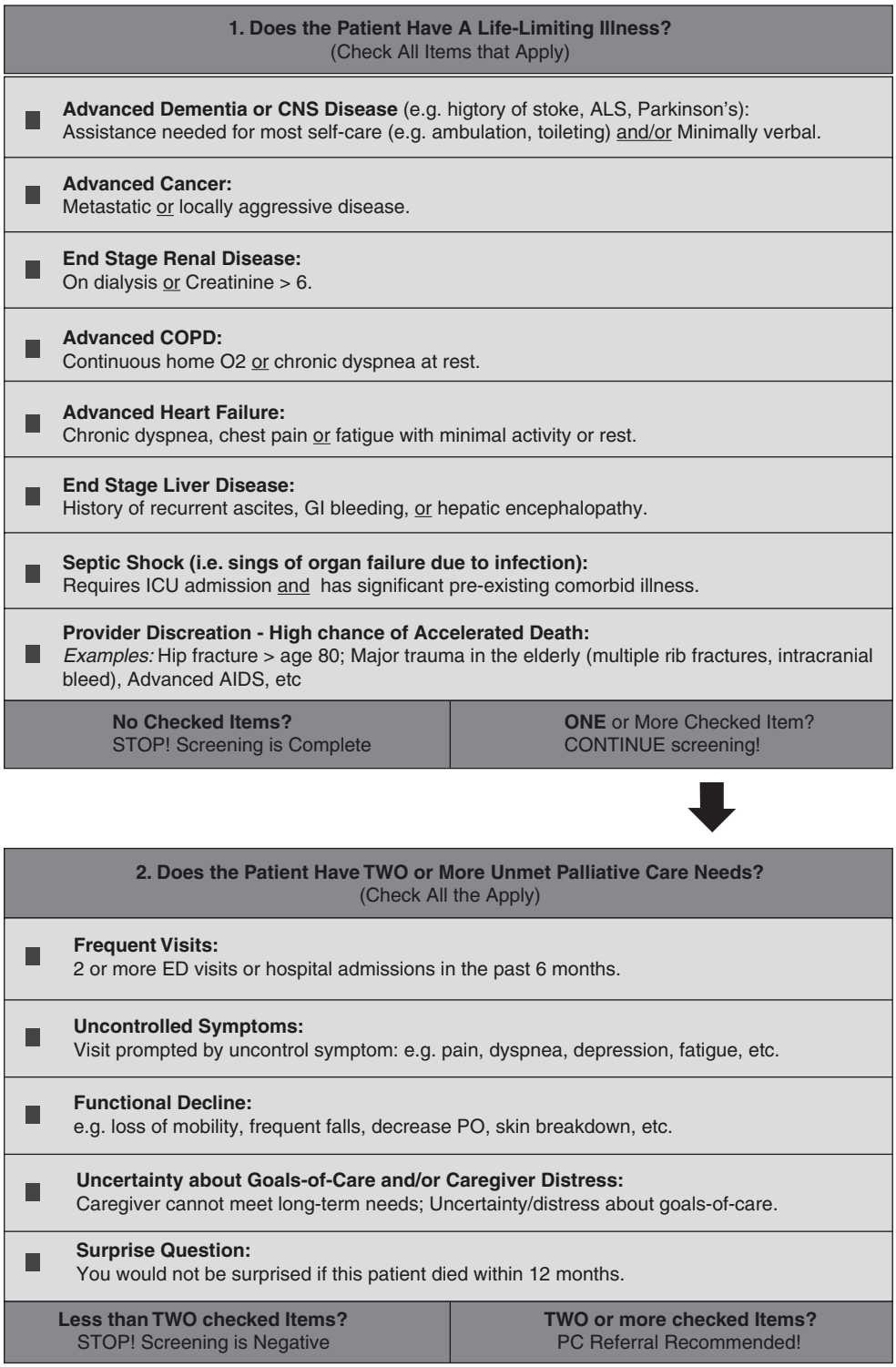

Fig. 62.1 Palliative care screening tool. (From George et al. [16], with permission Springer Nature)

Regardless of medical specialty, discussing prognosis with the patient is a challenge. The emotional and psychological impact of the information imparted and the lack of precision possible under most circumstances make it fraught [18]. For this reason, it is important to ask permission prior to sharing this information. If a patient or family is focused on prognosis, it is often useful to ask: "Why are you asking me about this now?" This will usually lead to the patient or family talking about their anxiety or fear, which you can then address. We provide prognosis in terms of "hours-to-days," or "days-to- weeks," or "weeks-to-months," or "months-to-years," with the provision that these are estimates. Using

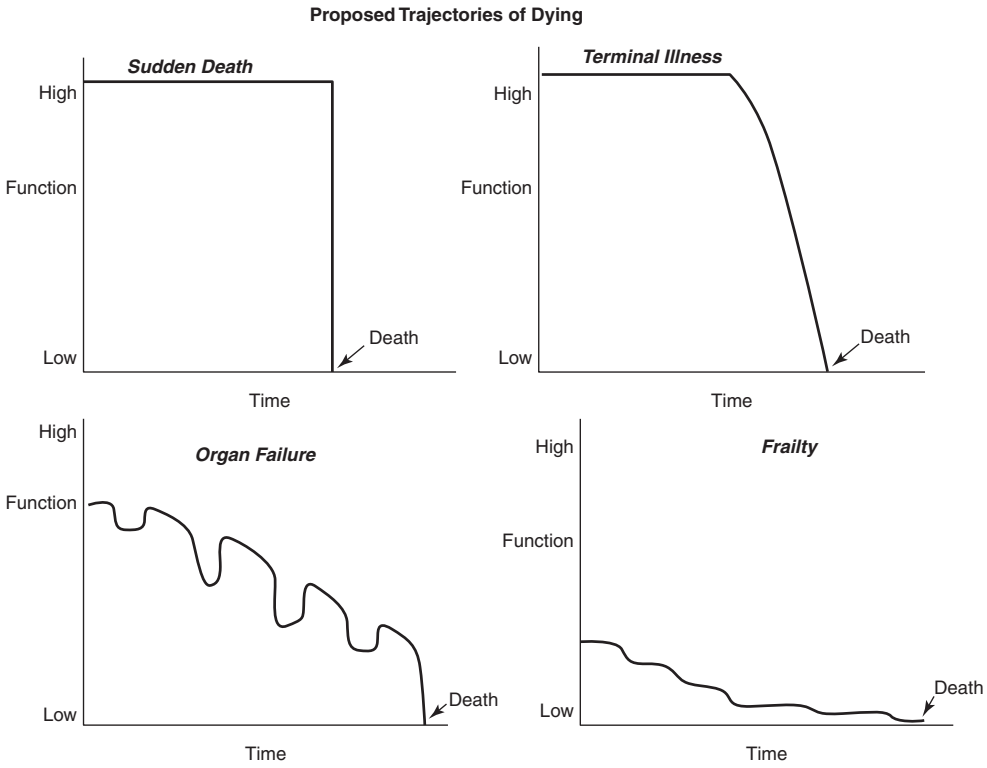

Fig. 62.2 Proposed trajectories of dying. (From Lunney et al. [19], with permission John Wiley & Sons)

specific numbers of hours, days, weeks, months, or years leaves more room for error and introduces potentially emotionally traumatic sequelae if the patient were not to live as long as forecast. Conversely, some patients and families will be upset if the patient lives beyond that estimation and perhaps express confusion and lack of faith in medical information.

When you find that further conversation is needed, you must set the stage and prepare. The emergency physician should facilitate communication among the various multidisciplinary teams involved in the patient's care. Palliative care teams, where available, can also assist in complex decision-making. Consider utilizing pre-existing decision tools to determine if a palliative care consult may be helpful [16–18].

The Building Blocks of Effective Communication

Preparation

Good communication begins prior to entering the room. Gather as much information as possible. Examine the medical record carefully. Make contact with the treating oncologist or primary doctor. Tell them what you have found. Ask what their goals are for the patient, and discuss your plan to discuss your findings with the patient. Tell the specialist your concerns and ask for their recommendation. You can tell your colleague the exact words you plan to use: for instance, "I am worried this cancer is progressing, I want to talk with you about the possibility of things not going the way we had hoped."

Capacity

Assess the patient's capacity. Medical decision-making capacity is the patient's ability to understand the benefits and risks of, and the alternatives to, a proposed treatment or intervention (including no treatment) [20–22]. Capacity is the basis of informed consent. If you feel the patient does have capacity, prepare them by asking permission to have a "difficult conversation." Tell them it will be helpful to have someone with them either in person or on the phone. It is generally recommended not to speak to the patient alone unless you have express permission from them. If the patient does not have capacity, or you are worried that they may be too emotionally burdened to have the conversation, find the legal next of kin.

Physical Space

Be sure that you have a quiet, separate place to have the conversation. Try to make it as private and comfortable as

Table 62.1 The REMAP Guide

Reframe	*What is your understanding of what the doctors have told you about your dad's health?* If their understanding differs from the clinical realities, consider a follow-up statement such as *Unfortunately, we are in a different place now. Is it okay if we talk more about what we are seeing and what the next steps may be?*
Expect emotion	Stop talking and listen! Consider responding to emotion directly. Examples include the following: *I can see you are really concerned about this. Is it okay if we talk more about what this means?* Or *I cannot imagine what it has been like to hear all this news.* Do not be afraid of silence
Map out the future	Try and identify what the patient's goals are before making any recommendations. *Given what we have just discussed about the illness your dad is dealing with right now, what do you think would be most important to him right now?* Or *thinking about what you dad put in his advanced directive and your knowledge of him as his loved one, is there anything he would want to avoid? What would his reasons be? What values in life are most important to him?*
Align with values	*Now that I have a better understanding of what is important to your father, let's talk more about treatment options*
Propose a plan	Give specific recommendations, rather than a menu of options. *From what you have told me, I recommend... How does that sound to you?*

Adapted with permission from VitalTalk https://www.vitaltalk.org/guides/transitionsgoals-of-care [23]

possible. Have tissues available. Have a planned strategy for how the conversation should unfold.

Take a moment, ground yourself, clear your mind of any prior encounters, and rid yourself of preconceived ideas. Make a conscious effort to focus on being an advocate for the patient and meeting them where they are in the journey of serious illness. Also, body language speaks volumes. Walk in, make eye contact, and introduce yourself. Sit down if possible, or if not, assume a pose that says you are not rushed. Allow the patient to speak for the first minute without interrupting.

Conversation Templates

Most of these difficult conversations follow a template, and steps can be tailored to the patient depending on their immediate need (Tables 62.1 [23] and 62.2 [14]).

Responding

Do we flinch internally when we hear a family say, "I want everything done" or "He is a fighter"? We must learn to recognize these statements as possible emotional responses rather than cognitive responses (Table 62.3) [24]. Instead of this putting an end to the conversation, we should explore what "everything" means to this particular family.

If we can respond to their emotions with inquiry and recognition instead of continuing to give medical information, we can open up dialogue in a way that will help the family process what is happening emotionally. Once their emotions are realized, often discussions about care can move forward. If not, best to continue resuscitative efforts as appropriate, and prepare the family for further discussions by the inpatient or palliative care teams.

Table 62.2 Approaching 5-min ED goals of care conversations systematically as a procedure

Phase	Action
Minutes 1–2	Elicit patient understanding of underlying illness and today's acute change If available, build on previous advance directives or documented conversations Acquire sense of patient's values and character (to help frame prognosis and priorities for intervention) Name and validate observed goals, hopes, fears, and expectations
Minutes 3–4	Discuss treatment options, using reflected language Continually re-center on patient's (not family's) wishes and values Recommend a course of action, avoiding impartiality when prognosis is dire
Minute 5	Summarize and discuss next steps Introduce ancillary ED resources (e.g., hospice/observation unit, social work, chaplain)

From Wang [14], with permission Elsevier

Effective Use of Silence

Sitting in silence may feel as though it goes against the grain of a provider's role in a dynamic conversation. Physicians may infer that a pause in the conversation means that there should be further explanation or that more active direction is needed. However, the use of silence and pauses in the conversation aids communication. Silence allows the patient or family time to process information, cope with associated emotions, and utilize the time to formulate next questions or communicate concerns. If a provider jumps in too soon to fill this proverbial "space," the patient and/or family may not have the opportunity to move through these steps, if needed. After a pause, it can be helpful to incorporate a "check-in" and offer to repeat any needed pieces of information. It is appropriate to also acknowledge the difficulty of absorbing the information proffered and to offer support.

Table 62.3 Responses to patients' and caregivers' reactions)

But he was doing great when I visited him last!	Medical	*He is now in septic and cardiac shock*
	Emotional	*I cannot imagine what a shock this is for you. Unfortunately he is very sick. He has a very serious infection and his heart is failing. We are all hoping for a different outcome, but we are worried that he is dying*
Do everything possible!	Medical	*Ok, we will do CPR, intubation, dialysis, and any other procedure*
	Emotional	*I hear you, and we will provide him with the most aggressive care. It sounds like this has been a hard/long journey and this is a terrifying time. Can I ask, has your father ever imagined his health worsening to what we see now?*
He needs a feeding tube for nutrition so he can get stronger!	Medical	*We know from studies that feeding tubes do not help in the end of life*
	Emotional	*Most people think of food as love. We think it is inhumane to withhold food from people we love. But your father's body is shutting down from his illness, and he does not feel hunger like he used to. Artificial nutrition is not the same as food and will not give him strength. A feeding tube in his stomach may deprive him of the joy of tasting his favorite foods. Can we talk instead about ways to increase his pleasure around the food he may want?*
You want me to pull the plug? You want me to stop/withdraw care? You want me to let him die?	Medical	*We will continue to do everything*
	Emotional	*I hear your concern. It feels like we are making this decision, but really it is his body that has decided. He is dying a natural death from this illness. I will do everything I can to aggressively make sure your father does not suffer as his body goes through the natural process of dying*

Adapted from Aberger and Wang [24], with permission Springer Nature

Language, Diversity, and Culture

These intense conversations are difficult in any language. If the patient only speaks a language you do not, it adds another layer of complexity. We find, of course, that live interpreters are best, if available. Family members should not be used for these sensitive conversations because often, as family members, they are subject to the emotional content of the information and might not be able to translate the conversation. If language line phones are the only option, it helps to prepare the interpreter for the type of discussion you are going to have as they can also become discomforted when discussing these sensitive topics, and it may help to organize the conversation.

Cultural considerations should always be explored. We find that no one is an expert on all cultures, but sensitivity and curiosity are essential. When in doubt, ask. Ask openly about custom or tradition. Apologize if you find you have overstepped or assumed incorrectly. Some cultures cannot talk about death directly, so exploring which words are acceptable may take an extra few minutes. This is essential in establishing trust and rapport.

Spiritual and Religious Considerations

Spiritual and religious needs are also diverse and should be explored. Here again, curiosity and sensitivity are key. Ask about needs, beliefs, and customs. Recognizing spiritual distress is also very useful in having these conversations. Often families will respond to our bad news or recommendations with the phrase, "We are hoping for a miracle." This is another phrase that may invoke our discomfort. If we can recognize and manage our own reactions, we can use the following communication protocol to open this statement up, thus broadening and continuing our discussion. It is called the AMEN protocol (Table 62.4): "Affirm, Meet, Educate, No matter what" [24, 25]. This is a powerful tool to keep the conversation going rather than continuing attempts to "solve an issue."

Table 62.4 AMEN communication tool for miracles [24, 25]

*A*ffirm/*M*eet and Reflect	Demonstrate respect and communicate empathy for what the patient/family values and wants
Learn more	Get curious and ask to hear more about the miracle, hopes, or values framed through the patient/family religious/cultural beliefs
Broaden the care plan	Determine what else is important so you can discuss different care plan options from the perspective of patient/family values and goals
*E*ducate	Educate about the medical situation and options
*N*o matter what	Reassure the family of your support no matter what happens

Case Studies: Starting with Common Dilemmas and Gradually Layering in Complexity

Case Study 1: The Rapidly/Actively Dying Patient

The patient is a 62-year-old male with metastatic lung cancer who presents with altered mental status. Labs show pancytopenia with a platelet count of 5. He becomes more lethargic and requires intubation. His pupils are unequal and you suspect an intracranial hemorrhage.

Approach to Goals of Care for the Actively Dying Patient

If the patient is declining rapidly, goals of care are needed quickly. Think briefly about the trajectory of their illness and where they fall on it. This will lead to an initial prognosis. We can use this prognosis to guide our discussions – if prognosis is hours to days, we likely need to start conversations now in the ED. Even if we proceed with full life support resuscitative measures, we need to initiate discussions about the strong possibility of further decline or death.

A useful mnemonic is ABCD [18]. We need to consider this when the patient is chronically ill, actively dying, or at the end stages of their illness.

A: Advanced directives: Does this patient have any? POLST, MOLST, prior PC involvement?
B: Better symptom management
C: Caregiver? Who is the next of kin?
D: Is the patient decisional?

You identify the family, including the next of kin. They state their loved one has been declining and he expressed the desire that "when my time comes, let me go." They are tearful but agree with your recommendation based on prognosis, and his past expressed wishes to the family for comfort measures only.

Communicating with the Family of an Actively Dying Patient

Studies confirm the importance of the explicit explanation of impending death signs and the importance of avoiding both vague explanations about future changes and excessive warning of sudden change [13, 26]. Research tells us that generally families also want to know a patient's relief of suffering, advice on how to care for the patient, allowance of time for the family to grieve, and that providers take care to ensure that family members cannot overhear conversations between the medical staff outside the room at the time of patient death [27].

Families will often have questions about what to expect – whether the patient can hear or is aware of their presence and if the patient is suffering due to a lack of nutrition or hydration. It is important to answer all these questions and concerns. We encourage families to spend time and speak to the patient with acknowledgement that the patient may hear or sense their presence. The patient's religious and cultural traditions may also offer resources. Social work and pastoral care also should be considered.

Case Study 2: Stable Patient with Progression of Disease

Breaking Bad News Worsening disease despite treatment [28, 29]

The patient is a 64-year-old male with past medical history of hypertension and colon cancer post resection with chemotherapy, years ago. He presents to the ED with cough and shortness of breath. He has no hemoptysis or fever but is tachycardic. You do a CT scan to rule out pulmonary embolism. No embolism is found, but multiple pulmonary nodules are seen, suspicious for metastatic disease.

Before You Go in the Room Preparation is key. Do a thorough chart check, or call his primary care provider or oncologist to confirm this is possibly a new disease progression. If you find no evidence showing prior metastatic disease, you have to discuss the results with the patient.

In the Room Make sure the patient has capacity and has support present or by phone. First ask broadly what they know about their cancer. As stated in the previous case, asking this sets where to begin the conversation [17, 23].

Some patients have an understanding that their cancer has returned or spread to other parts of their bodies. Other patients and family may believe the cancer is "cured" or in remission, or that the cancer has spread, but they believe that current treatment is curative rather than palliative. If they disclose this, you can ask about treatment. What do they hope to get out of their treatment?

Once you know where to begin the conversation, discuss the results simply. Often begin with a "headliner" [23] that is concise and gets the critical information across such as "I have the results from the CT, it looks like the cancer might have spread/returned/is getting worse." Using a VitalTalk "I'm worried…" statement [23] here can also be effective in conveying the results and your sympathy. Although you often need to give more information after this statement, pause for the patient's response.

Next, Gauge Where the Patient Is Emotionally

If there is tension or silence, you may need to circle back to discuss future steps. Tell the patient you will return. Alternately, if the patient immediately and rapidly begins asking questions, this may be part of an emotional response to the news. He may not want further medical details, but

fear and anxiety are driving him to ask. Name the emotion you are seeing.

When you gauge that he is ready to discuss disposition and plan, start by recognizing the difficult nature of the conversation: "Whenever you are ready, I'd like to discuss what's going to happen next" [23]. In addition, offer palliative and/or spiritual care services, explaining what they do and the essential support they can give in the difficult days/months ahead.

After Discussion

If the patient is not actively dying and is stable for transport, it may also be appropriate to consider transfer to a hospice inpatient unit or home hospice. Provide guidance to the family that it is possible the patient may die during transport with more specific information tailored to the individual patient's clinical condition and estimated distance/time in transport. Some family members may elect against transport for these reasons.

Case Study 3: Death Disclosure of Sudden and/or Unexpected Death

You receive a call from paramedics reporting a cardiac arrest in the field. On arrival, emergency medical service (EMS) providers state they found the 73-year-old male after an unwitnessed cardiac arrest at home. He was undergoing chemotherapy for prostate cancer. EMS states that the son found the patient not breathing this morning and called 911. EMS intubated him and began ACLS protocol with pulseless electrical activity on the monitor for 20 min. In the ED, you continued CPR for over 15 min without a return of pulses, and the monitor now reveals asystole. Your team pronounces the patient in the ED. The charge nurse informs you that the family has arrived and is in the waiting room.

Before You Go in a Room

Establish your Team. The ED is hectic; however, nurses, residents, and other staff involved in resuscitation often want to participate in family meetings. Calling outside staff that can assist with bereavement (e.g., spiritual care, chaplains, or counselors) may also be helpful when available. Discuss beforehand which team members will likely stay with family afterward for instructions or family support.

Set the Room. Quiet is often hard to come by in the ED, but a family room is ideal. Social worker's or nurse manager's offices can also suffice, depending on the size of the family. Have one of your team members or staff escort the family to a quiet place. The person placing family in the room should ideally not be you in order to avoid questions or forcing you to disclose news in the hallway or in front of other patients. Also, this staff member can identify a "head" of the family or next of kin. Staff can ask that designated loved one who they think should also be in the room when the meeting begins. In addition, this co-worker can report back to you who and how many family/friends there are and their current emotional state.

In the Room [23, 30]

Introduce. Introduce yourself to every person in the room. Find the lead family member and place yourself next to them; this will be the person you primarily interact with. First, ask what they know so far, for example, the son watching CPR in progress has a better understanding of the severity of their loved one than the son called at work by the nursing home stating, "Your family member was transferred to the ED." Asking this establishes where to begin the conversation.

Deliver. Then give a "warning shot" stating you have difficult news. Very briefly without jargon, describe what happened today. Usually the events can be summarized in no more than two to four sentences. When disclosing a death, use the word "died" and then pause for silence. Traumatic, sudden, or pediatric deaths often produce more raw emotional responses. These will be discussed in more detail shortly.

Comfort. Find phrases that you feel comfortable saying during this difficult conversation such as "I wish this hadn't happened," "I'm sorry for your loss," or "I can't imagine how you feel." Some physicians feel their expressions of sympathy sound contrived or even condescending. However, empathy can facilitate further dialogue with the bereaved and is usually appreciated.

After Discussion

Assist. After allowing loved ones to process the event, ask for any questions. Discuss next steps and hand off the conversation to one of your colleagues. Social workers or case managers can obtain more information about the patient. Nurses or patient assistants can accompany them to their loved one for viewing. Special instructions are needed for traumatic deaths, such as no touching the deceased. Sometimes law enforcement may need to further discuss the death with medical providers.

Hand Off. Leaving the room, especially when it is still full of emotional people, can be awkward. Introduce the staff that will stay behind, and ensure the team is available for any questions. If you are in a family room, you can offer the space to the bereaved to take their time to contact family, and delegate and discuss who and when (or if) a family member will see the deceased.

Case Study 4: Managing Requests to Withhold Information

Your patient is a 78-year-old female admitted from home with a chief complaint of shortness of breath and not eating for the past 2 weeks. Past medical history includes breast cancer s/p chemo, stopped 2 months ago due to weight loss and weakness. Patient is alert and oriented to person, place, and time. She says she is not hungry and just tired all the time. Her chest X-ray shows worsening metastatic disease in lungs.

You discuss the results first with her daughter, her primary caregiver and health proxy. Her daughter asks information not be disclosed to the patient.

Requests for non-disclosure can be complex and often reflect a family's member's efforts to protect the patient from emotional harm. The flow of information may have been agreed upon within the family already (e.g., the patient does not want to know), but we must explore this prior to making assumptions.

The following modified approach is proposed by Chaitin from the Palliative Care Network of Wisconsin [31]:

Before You Respond Remain calm and monitor your inner reactions. Explore the request for non-disclosure with curiosity. For clinicians this can be frustrating, but expressing how *you* feel can quickly end the conversation. Recognize and check your emotions. Remember, the calmer you remain, the more information you will obtain from the family as to why they do not want their loved one to be informed.

Gain Knowledge

Psychosocial and Cultural Aspects. Use open-ended questions to gain insight. "Can you tell me more about your request?" "How does your loved one [your family] typically handle difficult information?

The Disease Itself. Inquire what the patient knows about their disease. Does the family think the patient already knows or suspects the results and would rather not talk further about it? Or is the patient completely unaware? Frequently, both the family and patient may be frightened and attempt to protect each other by not talking about "bad news."

Plan. There is no one right way. As the clinician, you can recommend first asking the patient if she would like to know or discuss her health. If so, we prepare the family by reassuring them that we will be gentle and slow. We will share small pieces of information and continue to ask the patient permission to continue.

Ask the patient in a neutral way (e.g., listing options so the patient does not feel pressured to choose only one specific way). Having family present and rehearsing beforehand are also helpful so the family feels they still support the patient. For this case, "Your family brought you to the hospital because you were short of breath and not eating. We took tests to figure out why. Some patients want to know all their tests and results, others prefer the doctors talk with family about what is happening and how to best help them. What do you think?"

Case Study 5: When There Are Disagreements Among Physicians

An 83-year-old male presents with SOB, cough, fatigue, and weakness. PMH includes prostate cancer on chemotherapy. Chest X-ray today reveals worsening metastatic disease with new pleural effusion. In the past year, the patient has had multiple ED visits and admissions with a diagnosis of advanced metastatic disease and a pattern of overall decline. Patient shows little understanding of disease progression.

When questioned about his cancer, the patient states: "I am a fighter, and I'm going to beat it and be cured." When you speak with his oncologist, she feels the patient can live for years, and his chemotherapy overall is going well.

Before You Respond [32–34] When dealing with a response that is discordant, emergency clinicians must first remain calm and try to understand the other clinician's viewpoint. Sometimes in an established provider-patient relationship, there can be discrepancies in prognosis understanding. This can be due to several reasons (e.g., the clinician-patient bond) that make it difficult to acknowledge that the disease is progressing, regardless of treatment. Also sometimes patients can take away or naturally choose to accept only the positives during care discussions despite clinicians delivering information to the contrary.

Gain Knowledge Begin by using open-ended questions to gain insight on how the oncologist or primary clinician is interpreting the patient's status. Ask how past planning and prognosis discussions between him/her and the patient have progressed. Using "I'm worried" statements such as "I'm worried today that he's doing worse" can help "third space" the disease so the oncologist does not feel confronted or feel a sense of failure [23]. It is hoped that the oncologist can reflect on the overall trajectory of the patient's disease and give insight into the current negative results.

Plan State to the oncologist that you will share today's results with the patient and ask him/her: "Based on these results, how can we best help the patient?"

Acknowledge their difficulty in reframing their expectations for the patient such as "Seems like you have

known the patient a long time. This must be difficult for you." If the patient is not to be discharged, tell the oncologist that as the ED clinician, you want to include them in further plans. "Would you mind if I conferred with you in the next steps? From the ED, we are planning to...." In addition, state that you are consulting palliative care, stating they will provide an additional level of support during this admission. If the oncologist disapproves of the plan, remember: it is his/her opinion. Ultimately your obligation is to the patient, not the oncologist.

Case Study 6: Dying in Isolation

You care for a 63-year-old female with a chief complaint of shortness of breath, cough, and fever. She has a past medical history of COPD and lung cancer. She is alert and oriented, but hypoxic on room air and febrile. You are concerned about a COVID-19 infection. In the ED, the patient becomes more hypoxic and has increasing oxygen demands. She is ultimately intubated and awaits admission to ICU. The patient's family arrive several hours later, but are not allowed in. They beg for information about her condition and ask to see the patient.

Before You Discuss You first have to prepare for your meeting. Communication and goals of care conversations have evolved during COVID-19 due to the unpredictability of the pandemic. Communication between patients, clinicians, and family varies widely. Supporting a patient's loved ones can take place on voice or video calls as visitors are often not allowed. Communication tools are available from CAPC and VitalTalk for periods of social upheaval [23, 35]. These conversations are best led with an effort to first identify patient values. Recommendations regarding specific interventions such as mechanical ventilation or CPR can then be made. Having the family see the patient via video chat can be helpful in explaining the seriousness of illness or prognosis. Establishing regular video visits for family can help ease distress for both loved ones and the patient.

Case Study 7: Telephone Death Notification [36–38]

Your patient is in cardiac arrest in the ED. Resuscitation was unsuccessful. The patient is a nursing home patient with past medical history of colon cancer and dementia; it is unknown if the family has been informed. You call the next of kin.

Identify When calling next of kin, first introduce yourself, and inquire if the nursing home has already called. If this patient was admitted from home, ask if they knew the patient was in the hospital. Again, this gives you a marker for where to begin the conversation.

Clarify Sometimes the information can be incorrect, or the person listed defers to another family member. Therefore, first clarify the relationship between the patient and the person on the phone. State that the patient is seriously ill and ask if they are able to come to the hospital. Ask how and when they are arriving, and encourage them to have another person accompany them, if possible.

****If at this point the family member is unable to get to the ED and the news must be delivered over the phone, take the following steps. ****

Ability If information must be delivered over the phone, ask if they are somewhere where they can sit down and talk. If not (e.g., they are driving or in a public space) make a definitive time to call them back, sooner rather than later.

Headliner State you have difficult news. Briefly, in one or two sentences, summarize what happened before the patient reached the ED today. Gather this information from the patient's history.

Deliver Briefly state the patient's ED course and without using jargon, state the outcome. Using the word "dead" or "died" is essential. "We attempted to restart her/his heart and help her/his breathing with breathing tubes and medicines, but despite our best efforts your [name relation to patient] died. I'm sorry."

Pause Offer condolences. Resist the urge to fill the silence with medical information.

Support Once you feel they are able to discuss more, ask for any questions, and allow for their emotional reaction as a natural response to the news.

Case Study 8: Death of a Child [39, 40]

A 6-year-old male child was admitted in cardiac arrest. The child was found by her mother in bed unresponsive; CPR was started. The response time to the hospital was 10 min. In ED, CPR continued; the patient was intubated and ACLS performed, but the patient remained asystolic. His mother is able to tell you that he was born prematurely with a seizure disorder. At age 3 he developed asthma and then leukemia. He has had multiple admissions for his complex medical problems. His leukemia was in remission after several treat-

ments. Resuscitation efforts were continued without success for 10 min; you pronounced him dead at 9:04 a.m.

Before You Go in the Room The death of a child is tragic and traumatic for all involved in his care. 22% of pediatric deaths occur in EDs [39]; therefore it is likely that we will all experience this multiple times during our careers.

Establish a private place to inform loved ones, even in situations where the family witnessed the resuscitation. Have a staff member, not yourself, accompany the loved ones to a family room. It's important to avoid an emotional confrontation in the hallway or in front of other patients or children. This staff member can also identify the head of the family, limit who should be in the room, and describe the family's emotional state. Go in with a small team. Pediatric deaths affect everyone working in the ED, and having a few of your colleagues with you for the family discussion is helpful for everyone.

In the Room Introduce yourself and identify the staff members with you. Then, carefully and slowly, tell them you have tragic news. Be succinct, tell them despite your best efforts their little boy has died, and then pause.

Expect heightened emotional reactions [41, 42]. Most adults have the inherent need to protect children, so with the death of a child, their loss can sometimes manifest itself as a sense of shame. Rarely, this is acted out in anger. Always try to have colleagues present and a safe exit strategy from the room.

Other loved ones may have many questions surrounding the death, especially if it was unexpected. Listen carefully: do they need more information, or are they experiencing an emotional reaction? It is vital to continue to listen and convey your sympathy. Keep answers as short as possible. Assure families that they are not to blame for their loss. Expect the unexpected reaction. Keep the door open or unblocked in case of a violent or flight reaction from loved ones [41]. Realize anger is not directed at you personally. Most families will question their last interactions with their child and what they could have done differently. Bring a chaplain if available.

After Discussion After delivering the news, hold a debriefing session with your ED team. Team members need to understand their emotions, as well as help one another validate each other's reactions.

Some Additional Tips

Communicating with Children

We should use developmentally appropriate language to answer a child's questions about the condition of a loved one and the circumstances surrounding their absence from the home. It is crucial to tell children the truth and not craft a less alarming reason for their absence or illness/death, such as "Grandpa went to sleep" or "has a cold." This may result in the child having difficulty trusting adults in the future or becoming scared to go to sleep or alarmed when a loved one becomes ill [43].

Child life specialists and social workers can provide guidance under these circumstances and provide literature and education to parents dealing with difficult news. Palliative care teams often have staff specializing in pediatric needs.

Explore resources that are available for parents with the assistance of the ED interdisciplinary team. The "Parenting at a Challenging Time" or PACT program offers an online toolkit to support children of parents with a serious illness that includes communication tips (https://www.massgeneral.org/assets/MGH/pdf/cancer-center/pact-toolkit.pdf) [44].

It also may be helpful for parents to engage the counselor at their school and/or their pediatrician to provide ongoing counseling and support.

Communication at Sign Out

Important considerations at sign out are in addition to pre-existing checklists and required safety checks, such as name, location, and allergies, to name a few. We should include goals of care, capacity, next of kin, and plan of care (Table 62.5) [45, 46].

Takeaways: Keeping the Connection

In the ED, dealing with the "sickest of the sick" on a daily basis can be exhausting, especially to clinicians with limited training in delivering difficult news to patients/families, end of life care, or psychosocial care. For each low acuity patient that arrives in the ED, there might be two or three nursing home residents with "failure to thrive" or sepsis. Depersonalization, cynicism, and exhaustion can set in with studies showing emergency medicine clinicians at highest risk [47]. The challenge is to connect with our patients, maintain empathy, and be professional. To create a supportive environment for clinicians, there are four areas to consider: connection to patient's families through communication

Table 62.5 Tips for sign out/hand off [45, 46]

Any goals of care discussions to date and treatment plan
Time frame of a time limited trial of a particular treatment
Review of the surrogate medical decision-maker(s)/healthcare proxy and their corresponding contact information
Any contact and recommendations of outpatient providers, including the medical oncologist
Review of resources that have assisted with the care to date and their next steps, including palliative care consult
Most recent communication with the patient and/or family and outline of future updates or further discussion

skills; reflection of both self and department; and engagement with peers [47–51].

Reflection and Engagement [47, 48]

The ED works as a team; communicating with colleagues and other providers is essential. A natural response after a difficult case is to immerse ourselves in an endless pile of paperwork without reflection. To help counter these clinical work patterns, providers can adapt brief steps that can be incorporated into practice:

- *Debriefing* after every resuscitation or difficult case.
- *Moment of silence after every death*. No exceptions.
- *Leaving the department for a break on a clinical shift*. No matter how short.
- *Death Rounds*. Creating a ritual during faculty meetings or resident conferences around department deaths can also be useful for staff.

The Words We Use: Cultivating Patient-Centered Care

Our job in the ED is to determine what is best for our patients, medically and emotionally. Providing education on hospice and palliative medicine, which includes communication skills, to all ED clinicians including nurses, residents, and social workers, can focus care based on the patient's wishes. Find supportive palliative care staff who can champion patient-centered care within your department. Many education models exist. To launch this process clinically, you can begin by:

- *Using words* such as quality of life, patient's wishes, and comfort-focused care
- *Avoiding words* such as withholding, withdrawing, and phrases such as "nothing we can do"
- *Expressing* your thoughts and feelings when meeting with families and patients such as "I'm worried about…" or "I wish…" [23]

Actions such as these establish an environment of being conscientious and willing to engage. Integration of these communication skills and principles is realizing there is no magical finish line where all clinicians will gain resilience or cultural change. Rather, these practices require constant practice in order to maintain a "muscle memory" of patient-focused care.

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Palliative Care Research

63

Paul L. DeSandre and Gretchen E. Bell

Introduction

Research addressing the emergency department (ED) care of the seriously ill is growing. At the time of this writing, a simple PubMed (NLM) search for articles combining the "Title" terms "Palliative" and "Emergency" shows a marked increase since 2008 (Fig. 63.1). In order to better understand relevant historical studies and identify future directions for palliative care (PC) research in the ED, we expanded our search and identified three articles addressing research opportunities, priorities, and cancer-specific concerns. Those articles span a range of 10 years with common themes, providing the structure for this review of relevant research in the field.

The first of those three articles appeared in 2006 at the beginning of the increase in related publications. This article provides a list of research opportunities for emergency clinicians derived from consensus statements on end-of-life care from the 2004 National Institutes of Health state-of-the-science conference and the National Institute of Nursing Research 2006 Areas of Research Opportunity [1]. The next article, published in 2011, defined a set of research priorities for PC in the ED. These priorities for research were the product of an expert consensus workgroup conference titled "Improving the Quality and Efficiency of Emergency Care Across the Continuum: A Systems Approach," sponsored by the Agency for Healthcare Research and Quality (AHRQ) and the American College of Emergency Physicians (ACEP). From this workgroup, four key research questions emerged: Who are the patients requiring PC in the ED? What is the role of the emergency clinician for these patients? What is the impact of PC integration in health care utilization? What are the educational priorities?

The six categories of research priorities proposed to address these questions were descriptive, attitudinal, screening, outcomes, resource allocation, and education of clinicians [2]. The third article, from 2016, offered a specific research agenda for the emergency care of patients with cancer. In this agenda, important PC research needs focused on addressing health care use and patient management [3]. For this chapter, in order to include a broader perspective beyond cancer patients in the ED, we use the six categories of research priorities from the second article as a framework. We provide further categorization using evidence-based medicine terminology to describe research methods as described by Greenhalgh [4]. With this combined structure, our goal is to present essential information on the growing body of research devoted to improving the care of patients with serious illness in the ED (Table 63.1).

Descriptive Studies

Descriptive studies of PC in the ED provide information on existing characteristics of patients, circumstances of their care, and unmet needs. Studies of this type began around 2002 with substantial increases in recent years. The vast majority of these studies are of cohort design. Descriptive studies should provide an accurate depiction of patients with serious illness and their prehospital and ED experience. In reviewing the related literature, four categories emerge: (1) general PC; (2) cancer; (3) pediatric PC; and (4) coordination and access to care.

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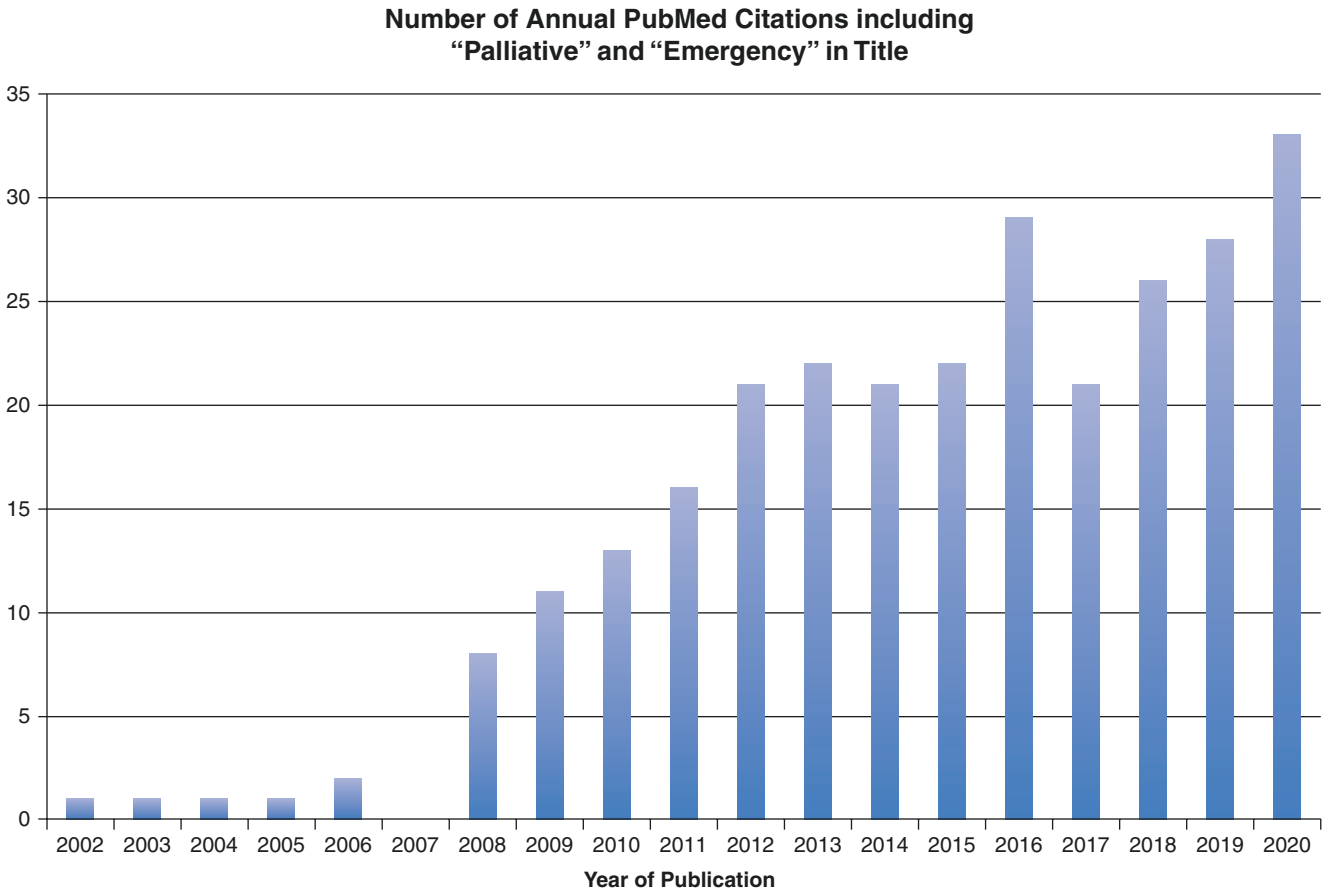

Fig. 63.1 Search of PubMed (National Library Medicine) for articles combining the "Title" terms "Palliative" and "Emergency" showing a marked increase since 2008

General Palliative Care

While the range of topics is broad and the methods variable, general descriptive PC research has focused on defining patient characteristics and the provision of PC in the ED. Two systematic reviews describe available findings, one in 2015 [5] and another in 2019 [6]. The first addresses the prevalence of advance directives in the ED. The second describes the impact of PC services on ED use. In the first article, Oulton et al. found an overall low rate of advance directives completion with wide variation. Certain variables were associated with a higher likelihood of completion of advance directives. These included patients who were older, were in poor health, belonged to a specific religion, were widowed, had children, were a resident of an institution, or had a primary care provider. These characteristics suggest awareness and understanding of the consequences of illness, which may have encouraged the completion of advance directives at some point prior to needing ED evaluation. The second systematic review by Bone et al. looked at the impact of PC services on ED use and found that the provision of PC or hospice services was associated with lower ED use in the last year of life for patients ≥65 years of age. The majority of included studies were from the United States with almost no information from low- to middle-income countries.

The remaining publications were of either cohort or cross-sectional design. These articles address the range of models of provision of care and the substantial PC needs in the ED. Quest, et al. describe four types of ED PC integration based on 11 successful programs: traditional consultation, basic integration, advanced integration, and ED-focused advanced integration [7]. A 2010 single-site cross-sectional survey of 50 functionally impaired adults ≥65 years old in the ED found the majority of patients exceeded severity of needs assessments for physical symptoms, finances, mental health, and access to care [8]. In 2012, patients dying in EDs in France and Belgium were reported as having a lack of palliative interventions despite 80% having died in the context of withholding or withdrawing of life-sustaining interventions [9]. From the same year, a US study from a large urban ED reported that 84% of the patients seen by PC consultants died while in the ED. Common patient characteristics for consultation included young age, sudden critical illness or traumatic event, or were imminently dying [10]. Yet another

Table 63.1 Palliative care research in the emergency department [2, 4]

Research priority[a]	Year	First author	Objectives	Type of Study[b]
Descriptive				
General palliative care	2015	Oulton [5]	Determine the prevalence of ADs among ED patients, with a focus on older adults, as well as factors associated with rates of AD completion	Systematic review
	2019	Bone [6]	Review factors associated with ED attendance during the last year of life in older adults	Systematic review
	2013	Quest [7]	Describe clinical examples of ED and PC integration, including ED-provided subspecialty PC practice	Cross-sectional
	2010	Grudzen [8]	Identify the palliative care needs of seriously ill, older adults in the ED	Cohort
	2012	Van Tricht [9]	Describe proportion of dying patients who received PC in the ED	Cross-sectional
	2012	Lamba [10]	Describe most commonly requested ED-PC services and understand why ED-PC consults are currently requested	Cohort
	2017	Blackwell [11]	Critique the feasibility of experience-based co-design of a methodology for quality improvement interventions to improve PC experiences in the ED	Qualitative: experience-based co-design
	2015	George [12]	Develop a simple content valid screening tool for use by EPs to identify patients with significant PC needs and establish content validity	Qualitative: modified Delphi technique with expert panel
	2019	Köstenberger [13]	Determine the prevalence of patients presenting with palliative symptoms in an Austrian ED	Cohort
Cancer	2020	Chen [14]	Describe characteristics of cancer patients who utilize emergency medical services	Cohort
	2010	Barbera [15]	Describe the most common reasons for visits made to the ED during the final 6 months and the final 2 weeks of life in patients who die of cancer	Cohort
	2011	Mayer [16]	Examine why patients with cancer present to the ED	Cohort
	2015	Henson [17]	Explore factors associated with ED attendance by cancer patients in their last month of life	Systematic review and meta-analysis
	2016	Elsayem [18]	Examine the presenting symptoms associated with risk of ICU admission and hospital death in patients with cancer admitted through an ED	Cohort
	2017	Rivera [19]	Estimate the proportion of ED visits made by cancer patients, understand their clinical presentation and examine factors related to inpatient admission. National dataset	Cohort
	2018	Henson [20]	Identify socioeconomic and clinical factors associated with ED attendance at EOL and the relationship with prior ED use among cancer decedents	Cohort
	2019	Caterino [21]	Understand common characteristics of patients with cancer seeking emergency care and identify opportunities for care optimization	Cohort
	2019	Verhoef [22]	Compare EOL trajectories of hematologic malignancy and solid tumor patients who died <3 months after ED visit	Cohort
Pediatric palliative care	2018	Gaucher [23]	Describe the characteristics of pediatric PC patients with pediatric ED visits	Cohort
	2018	Rocha [24]	Identify factors associated with emergency visits and hospitalizations in patients with congenital syndrome of Zika virus. Identify the clinical interventions performed from the PC perspective	Cross-sectional
Coordination and access to care	2002	Ausband [25]	Determine the prevalence of PC protocols among EMS agencies in the United States and what proportion of the population is covered by those protocols	Cross-sectional
	2014	Carron [26]	Describe situations where prehospital physicians managed PC situations	Case report
	2013	Wallace [27]	Identify patients receiving specialist PC services who attend the ED and determine if these presentations are potentially avoidable	Cohort
	2013	Hjermstad [28]	Register the reasons patients with advanced cancer attend the ED, the interventions performed during their hospital stay, and symptom intensity upon admission and discharge. Assess patient attitudes toward ED attendance	Qualitative: mixed cohort and structured interviews
	2018	Kao [29]	Investigate the factors for ED use during out-of-hours periods of palliative home care services among advanced cancer patients	Cohort
	2018	Lipinski [30]	Evaluate the use of PC services in patients with heart failure who present to the ED	Cohort

(continued)

Table 63.1 (continued)

Research priority[a]	Year	First author	Objectives	Type of Study[b]
	2019	Green [31]	Examine the decision-making process that leads to patients with palliative care needs to seek emergency care	Qualitative: narrative interview
	2014	Shin [32]	Compare the symptom burden and survival rate of patients admitted to an acute palliative care unit from an ED to those transferred from an inpatient unit	Cohort
	2017	Spilsbury [33]	Determine how the association of community-based PC with ↓ED visits in the last year of life varied by patient factors	Cohort
Attitudinal				
Provision of palliative care in the ED	2009	Wiese [34]	Explore the attitudes and beliefs of prehospital EPs about their experiences in dealing with PC patients in out of hospital emergency situations	Cohort
	2012	Gruzden [35]	Explore attitudes and beliefs among attending EP's provision of PC services in ED	Qualitative: semi-structured focus groups
	2013	Lamba [36]	Elicit the perceived barriers by EP to providing PC in the ED	Cross-sectional
	2015	Weil [37]	Explore the understanding of PC by healthcare professionals caring for patients with advanced cancer attending the ED	Qualitative: focus groups and semi-structured interviews
	2019	Côté [38]	Propose implementation strategies for pediatric palliative care in the ED	Qualitative: semi-structured focus groups
	2009	Smith [39]	Explore the attitudes, experience, and beliefs of EPs about PC in the ED	Qualitative: focus groups
	2015	Russ [40]	Investigate staff experience and attitude toward PC provision in a public metropolitan ED	Cross-sectional
	2018	Wright [41]	Identify EP's priorities for improvement in ED-based PC for older adults	Qualitative: semi-structured interviews
	2013	Grudzen [42]	Identify hospital level factors from the administrative perspective that affect the availability and delivery of PC services in the ED	Qualitative: semi-structured interviews
	2015	Rivera [43]	Explore the perceptions and barriers encountered by practicing EPs in providing PC in Puerto Rican EDs	Cross-sectional
	2019	Argintaru [44]	Describe perceived barriers and facilitators to GOC discussions by EM physicians/residents	Cross-sectional
	2010	Smith [45]	Understand the experiences of acutely symptomatic, terminally ill patients seen in the ED	Qualitative: semi-structured interviews
	2018	Cooper [46]	Raise awareness of the experience of PC patients and families/caregivers together with the insights of clinicians caring for them increasing understanding of why implementation of good practice remains difficult	Systematic review
	2019	Di Leo [47]	Explore issues with delivering ED-PC from the perspective of both providers and patients	Qualitative: focus groups and semi-structured interviews
End-of-life care in the ED	2017	Fernandez-Sola [48]	Define the attributes of dignity in EOL care in the ED, based on the opinions of physicians/nurses	Qualitative: focus groups and semi-structured interviews
	2019	Giles [49]	Examine the experiences, perceptions, and needs of nurses providing EOL care in the ED setting in relation to sudden and unexpected deaths	Qualitative: descriptive survey
	2019	Alqahtani [50]	Explore challenges from a staff perspective of safe appropriate high-quality EOL care for people diagnosed with non-malignant diseases who present to the ED	Systematic review
	2020	Mughal [51]	Describe, understand, and explain the perceptions of ED nurses on provision of EOL care	Systematic review
Educational needs	2011	Meo [52]	Characterize the level of formal training and perceived educational needs in PC of EM residents	Cross-sectional survey
	2012	Lamba [53]	Characterize EP's perceived educational and formal training needs for PC-related skills	Cross-sectional survey

Table 63.1 (continued)

Research priority[a]	Year	First author	Objectives	Type of Study[b]
Screening				
General	2020	Kistler [54]	Identify existing triggers for PC consult, how they compare between settings, and common criteria used to identify those in need of PC consult	Systematic review
	2008	Mahony [55]	Identify chronically ill older patients with PC, homecare or hospice needs, and ↑ linkage with these services	Cohort
	2016	George [56]	Evaluate the methods, tools, and outcomes of PC screening and referral projects in the ED	Systematic review
	2001	Mion [57]	Improve case finding of at-risk older adults and provide comprehensive assessment in the ED setting with formal linkage to community agencies	Cohort
	2011	Glajchen [58]	Improve PC referral among frail, elderly patients in the ED	Cohort
SPEED	2011	Richards [59]	Develop and validate a novel palliative medicine needs assessment tool for patients with cancer in the ED	Cohort
	2019	Reuter [60]	Assess the feasibility and reach of a novel care pathway utilizing electronic health record embedded screening and automatic triggered consultation to deliver ED-based palliative care services for patients with active cancer	Cross-sectional
P-CaRES	2015	George [12]	Develop a simple content valid screening tool for use by EPs to identify patients with significant PC needs and establish content validity	Qualitative: modified Delphi technique with expert panel
	2016	Bowman [61]	Assess acceptability and reliability of a brief novel content – validated screening tool for unmet palliative care needs – the Palliative Care and Rapid Emergency Screening (P-CaRES) Project, a brief novel content among EPs of different roles and experience levels	Cross-sectional
	2017	Ouchi [62]	Assess the performance and determine the acceptability of a content-validated palliative care screening tool	Cohort
	2020	Tan [63]	Optimize the use of electronic health records by creating a clinical decision support (CDS) tool to identify the high-risk patients most likely to benefit from primary PC and provide point-of-care clinical recommendations	Qualitative: focus groups and survey
Surprise question	2018	Ouchi [64]	Evaluate the prognostic value of the suprise question (SQ) in elderly ED (>65) patients for predicting 12-month mortality	Cohort
	2019	Verhoef [65]	Evaluate the prognostic value of the surprise question (SQ) in patients with advanced cancer visiting the ED and study the yield of adding other predictors for approaching death	Cohort
	2019	Aaronson [66]	Evaluate the prognostic value of the SQ in symptomatic heart failure patients presenting to the ED	Cohort
	2019	Ouchi [67]	Determine the association of the surprise question with actual 1-month mortality among undifferentiated older adults admitted from the ED	Cohort
	2019	Haydar [68]	Determine the utility of the modified SQ (30 days versus 1 year) to predict in-hospital mortality and resource utilization for hospitalized ED patients	Cohort
Other ED screening projects	2014	Ouchi [69]	Observe prevalence of ED-initiated palliative care consultation for advanced dementia following quality improvement intervention	Cohort
	2015	Kistler [70]	Evaluate the impact of ED-initiated palliative care referral on the proportion and timing of consultation	RCT
Outcomes				
General	2019	Grudzen [71]	Measure the impact of primary PC education for ED providers on disposition, healthcare utilization, and survival times	RCT
	2020	Yash [72]	Measure the current quality of EOL care in ED to identify gaps, formulate improvements, and implement the improved EOL care protocol	Cohort
	2014	Lamba [73]	Highlight needs and opportunities for better integration of EM and PC	Expert opinion
	2016	da Silva Soares [74]	Examine the effectiveness of ED-based PC interventions on hospital admissions, LOS, symptom severity, QOL, use of other healthcare services, and PC referrals for adults with advanced disease	Systematic review
	2020	Wilson [75]	Assess the effect of ED-based PC interventions on patient- and family-reported outcomes, healthcare utilization, and survival for adult patients	Systematic review

(continued)

Table 63.1 (continued)

Research priority[a]	Year	First author	Objectives	Type of Study[b]
Traditional model of consultation	2016	Delgado-Guay [76]	Assess the effect of ED-PC consultation in advanced cancer patients on time to PC consult, symptom intensity, LOS, and disposition	Cohort
	2019	Mogul [77]	Investigate the resource utilization and mortality of patients age ≥65 from long-term care facilities who present as emergency severity index level 1 (most urgent)	Cohort
	2019	El Majzoub [78]	Examine the association between timing of palliative care consult and in-hospital mortality in admitted cancer patients	Cohort
Basic integration	2016	Grudzen [79]	Assess the effects of ED-initiated PC consultation in patients with advanced cancer on QOL, depression, healthcare utilization, and survival	RCT
	2016	Highet [80]	Evaluate the feasibility of a focus intervention in the ED to identify hospice-eligible patients and facilitate disposition	Cohort
	2019	Koh [81]	Study the feasibility of a three-way model of care between the ED, inpatient PC team, and hospice services designed to increase early access to palliative care	Cohort
Advanced integration	2019	Tiernan [82]	Evaluate if a multifaceted intervention composed of flagging known patients, screening tool, proactive palliative medicine engagement in the ED, and educational programming impacts palliative care referral rates or healthcare utilization metrics	Cohort
	2017	Weng [83]	Improve the quality of care for ED patients at EOL using PC champions, education, and close collaboration with a hospice team	Cohort
ED-focused advanced integration	2013	Rosenberg [84]	Describe an approach in expanding the role of ED staff into palliative and EOL care	Case report
	2015	Grudzen [85]	Transform geriatric emergency care by applying PC principles via a multi-step process improvement	Cohort
	2018	Liberman [86]	Investigate the effectiveness of an Advanced Illness Management program in the ED on improving outcomes	Cohort
End-of-life care	2008	Sedillot [87]	Describe a five-step protocol for withholding and withdrawing of life support in an ED for terminally ill patients	Cohort
	2013	Shlamovitz [88]	Discuss palliative sedation in the ED and the use of ketamine	Case report
	2019	Wang [89]	Discuss best practice through a systematic approach to comfort care transitions in the dying ED patient	Overview: non-systematic review
	2019	Economos [90]	Assess the appropriateness of EOL care provided to actively dying patients in the ED	Cohort
	2019	Chor [91]	Describe the epidemiological characteristics, symptom burden, and management of patients using a protocolized management care bundle	Cohort
	2020	Ruangsomboon [92]	Assess whether high-flow nasal cannula is superior to conventional oxygen in relieving dyspnea in PC patients in the ED with do not intubate (DNI) status	RCT
Communication	2018	Mills [93]	Evaluate the utility to doctors of a form specifically designed to guide and document GOC discussions at point of care	Cohort
	2019	Hanning [94]	Determine which patients benefit, requirements, content, documentation, and harms and benefits for ED GOC discussions	Systematic review
	2019	Ouchi [95]	Describe development of a brief negotiated interview ED intervention to increase engagement in serious illness conversation by seriously ill older adults and describe its acceptability	Cohort
	2018	Leiter [96]	Assess whether trained EPs can administer a structured brief negotiated interview intervention to facilitate advance care planning conversations with high fidelity	Cohort
Resource allocation				
Community-based	2020	Taylor [97]	Evaluate PC initiatives which may avoid or shorten hospital stay at the end of life and analyzed their success in terms of reducing bed days	Overview: non-systematic review
	2008	Wiese [98]	Demonstrate the influence of PC teams on emergency calls by cancer patients or their relatives during the last 6 months of life	Cohort
	2016	Obermeyer [99]	Compare patterns of ED use and inpatient admission rates for elderly adults with cancer with a poor prognosis who enrolled in hospice to those of similar individuals who did not	Case-control

Table 63.1 (continued)

Research priority[a]	Year	First author	Objectives	Type of Study[b]
	2017	Sutradhar [100]	Examine the association between palliative versus standard homecare nursing and the rate of high-acuity and low-acuity ED visits among cancer decedents during their last 6 months of life	Cohort
	2018	Hirvonen [101]	Explore the effect of regional efforts to develop EOL care pathways and the availability of outpatient palliative clinic on the number, quality, and outcome of ED visits toward the EOL for patients with cancer	Cohort
	2013	Lamba [102]	1. Review four case scenarios that relate to palliative care and may be commonly encountered in the out-of-hospital setting 2. Provide a road map by suggesting four things to do to start an EMS-palliative care initiative in order to optimize out-of-hospital care of the seriously ill and increase preparedness of EMS providers in these difficult situations	Expert opinion
	2009	Wiese [103]	Explore the attitudes and beliefs of prehospital emergency physicians about their experiences in dealing with PC patients in out of hospital emergency situations	Cohort
	2017	Montgomery [104]	Develop an innovative strategy to provide collaborative care in the home to alleviate symptoms and avoid transport	Cohort
	2019	Kamphausen [105]	Investigate challenges faced by EPs who provide prehospital emergency care to patients with advanced incurable diseases and family caregivers in their familiar home environment	Qualitative: semi-structured interviews
	2019	Patterson [106]	Explore the extent to which access to, and quality of, patient information affects the care paramedics provided to patients nearing end of life and their views on a shared electronic record as a means of accessing up-to-date patient information	Qualitative: semi-structured interviews
	2017	McQuown [107]	Evaluate which patients presenting to the ED had their DNR status recognized by the physician and DNR orders that were made during their hospital stay	Cohort
	2016	Lakin [108]	Assess ED physicians' experiences with advance care planning electronic medical record documentation and their documentation needs	Cross-sectional
	2020	Vranas [109]	Evaluate how POLST form completion, treatment limitations, or both influence intensity of treatment among patients who present to the ED	Cohort
Within the ED	2015	Purdy [110]	Investigate the impact of the Marie Curie Cancer Care Delivering Choice Programme on place of death and hospital usage (ED and admissions)	Cohort
	2016	Lafond [111]	Improve the environment for EOL care of terminal ED patients	Cohort
	2020	Liberman [112]	Investigate the effectiveness of an artificial intelligence management program in the ED on key outcomes	Cohort
	2020	Chidiac [113]	Describe a system designed to optimize PC provision beyond specialist services during COVID-19	Expert opinion (letter to the editor)
	2020	Fausto [114]	Describe a multifaceted strategy to implement high-quality palliative care in the context of the COVID-19 pandemic that incorporates conventional, contingency, and crisis capacity	Expert opinion
After the ED	2020	Lee [114]	Examine the clinical characteristics and outcomes of patients who received intervention by a novel COVID-19 palliative care response team, focused on providing high-quality goals-of-care conversations in time-critical situations	Case series
	1999	Ting [117]	Study the early impact of bereavement and evaluate the effectiveness of the bereavement care given by a multidisciplinary team to close relatives of a sudden death, measured by the intensity of grief reaction (Texas Revised Inventory of Grief)	Cohort
	2019	Cooper [118]	Describe the implementation of ED Grief Support, a program developed to extend care to the bereaved through in-person, telephone, and e-mail follow-up for 1 year after the death of a loved one	Cohort
Education for clinicians				
Death disclosure	2002	Quest [119]	Design, implement, and evaluate a multidimensional, interdisciplinary, educational training module that enables residents to deliver an effective and empathic death disclosure in the emergency setting	Cohort

(continued)

Table 63.1 (continued)

Research priority[a]	Year	First author	Objectives	Type of Study[b]
	2006	Quest [120]	Explore the validity and reliability of the affective competency score (ACS), compared to a global rating measure to predict overall competency to perform a death disclosure in a standardized patient exercise and investigate useful thresholds of the ACS	Cohort
	2005	Hobgood [121]	Improve resident confidence, competency, and communication skills when delivering a death notification using the GRIEV_ING mnemonic	Cohort
	2013	Hobgood [122]	Improve the confidence, competency, and communication skills of EMS personnel in death notification using the GRIEV_ING mnemonic	Cohort
EPEC-EM	2010	Gisondi [123]	Assess adaptation of a comprehensive training course in palliative and end-of-life care for an emergency medicine residency. Compare asynchronous versus synchronous learning adaptations	Case-control
	2010	Ponce [124]	Study the feasibility and utility of an educational intervention designed to improve prehospital provider comfort with family witnessed resuscitation and death notification	Cohort
	2012	DeVader [125]	Assess resident knowledge, comfort, and proficiency in key palliative/hospice care principles and whether this can be improved via a brief education intervention	Cohort
	2018	Goldonowicz [126]	Investigate the value of a novel simulation-based palliative care educational intervention within an EM residency curriculum	Cohort
Training efforts	2016	Kraus [127]	Assess formal education on palliative care domains in emergency medicine residency programs and assess barriers/opportunities for further integration	Cross-sectional
	2019	Baylis [128]	Describe the number of Canadian postgraduate EM training programs with palliative care curricula	Cross-sectional
	2018	Shoenberger [129]	Define content areas and competencies for HPM primary-level practice in the ED	Expert opinion
	2019	Gruzden [71]	Measure the impact of primary palliative care education for ED providers on disposition, healthcare utilization, and survival times	RCT

Legend of abbreviations: *AD* Advanced directive, *COVID-19* Coronavirus disease 2019, *ED* Emergency department, *EOL* End of life, *EP* Emergency physician, *EPEC-EM* Education in Palliative and End-of-Life Care for Emergency Medicine, *ICU* Intensive care unit, *LOS* Length of stay, *PC* Palliative care, *P-CaRES* Palliative Care and Rapid Emergency Screening, *QOL* Quality of life, *RCT* Randomized controlled trial, *SPEED* Screen for Palliative and End-of-life care needs in the Emergency Department, *SQ* Surprise question

Research priority[a]

1. Descriptive
2. Attitudinal
3. Screening
4. Outcomes
5. Resource allocation
6. Education for clinicians

Type of study[b]

I. Quantitative studies
   1. Systematic review and meta-analysis
   2. RCT with definitive results
   3. RCT with non-definitive results
   4. Cohort studies
   5. Case-control studies
   6. Cross-sectional studies
   7. Case reports

II. Qualitative studies

III. Other
   1. Overview: non-systematic review
   2. Expert opinion

study from 2012 compared a month of ED-initiated PC consultations 4 years apart in a large urban ED in the United States. They found that most patients were admitted through the ED, yet consultations initiated in the ED were only 3% in 2005 and 6% in 2009 [11]. A similar study from 2019 assessed ED patients with unmet PC needs in Austria, based on a previously validated screening tool [12], with only 5.5% receiving PC consultation [13].

Cancer

In the cancer population, most of the descriptive studies focus on patient characteristics and ED use. One study showed the prehospital Emergency Medical Service (EMS) use in cancer patients appears to be greater among older patients, those with higher acuity, CNS cancers, or neurological or cardiac symptoms [14]. Lung cancer is consistently

found to be the most common type of presenting cancer, as well as the cancer most likely associated with in-patient death following ED use. Overall, lower socioeconomic status and symptom distress, particularly pain and dyspnea, are among the most common reasons for ED presentation [15–20]. In a 2019 multicenter prospective cohort study from 18 EDs, Caterino et al. found that nearly half of cancer patients presenting to the ED were ≥65 years old, and those presenting with uncontrolled pain from outpatient settings were associated with only 8% of specialist PC involvement [21]. Comparing hematological to solid tumor malignancies, those with hematological malignancies appear to have a substantially higher likelihood of in-hospital, ICU, and ED death [22].

Pediatric

There is a relative paucity of descriptive research addressing pediatric PC in the ED. Two 2018 studies, one from Canada and the other from Brazil, demonstrate missed opportunities and the need for greater access and collaboration. The Canadian study is a retrospective review of patients followed by the pediatric PC team who presented to their ED. Of the 290 patients studied, 40% died during that hospitalization with nearly 20% dying within the first 72 hours of admission. Two-thirds had completed advance directives on arrival to the ED, but less than 40% had goals of care discussions within that hospitalization [23]. The Brazilian study assessed patients presenting to the ED with congenital Zika virus syndrome. Affected children have a limited lifespan and require frequent ED visits, hospitalizations, and aggressive procedures throughout their life. Of the 92 patients followed in their specialty clinic who presented to the ED, only two hospitalized patients received PC specialty consultation [24].

Coordination of Care and Access to Palliative Care

The remaining descriptive articles of PC in the ED come from a variety of international sources examining access and coordination of care. Two publications studied emergency medical service (EMS) issues. The first, in 2002, surveyed a cross section of EMS agencies from 121 of the 200 most populous US cities and found only 5.8% of those agencies had protocols to care for patients with PC concerns [25]. The other article from 2014 used case reports to encourage increased PC education for EMS personnel and improved collaboration with healthcare systems [26].

Five studies from several different countries demonstrate a need for better access to PC services, particularly after usual business hours and even when previously connected to outpatient PC services [27–31]. One of these studies reviewed medical records of 500 heart failure patients presenting to two EDs in Canada during an 8-month period in 2013. Among those who died within 1 year, 41% received specialist-level PC, and 76% of those patients received services only in the last 2 weeks of life [30].

Two remaining descriptive studies showed benefits of PC specialty involvement. The first compared characteristics of patients directly admitted to an inpatient acute PC unit directly from the ED (12% of 2568 patients) versus those admitted elsewhere in the hospital. They found that while the ED patients had higher symptom burden and higher medical acuity on admission to their unit, they were more likely to be discharged to the community alive [32]. The second article used a regional Australian database of deceased patients with serious illness and found a 50% reduction in ED use in the last year of life for those enrolled in the PC community-based programs versus those not enrolled in these programs [33].

Attitudinal Studies

Studies exploring attitudes and perceptions of PC in the ED have identified barriers to care and opportunities for improvement. Nearly all related studies have occurred within the past decade. The majority of these studies viewed the provision of PC in the ED through the lens of healthcare workers, patients, and caregivers. A smaller number of studies focus specifically on end-of-life care, and the remainder target emergency medicine resident training needs.

Provision of Palliative Care in the Emergency Department

An early study assessed the emergency care of patients with PC needs from the perspective of 150 prehospital emergency physicians in Germany. A large majority (89%) reported experience with patients having advanced cancer with acute PC needs, but half were uncomfortable with the associated psychosocial challenges and felt that additional training would be useful [34]. Within the ED, several studies investigated PC-related attitudes of healthcare workers. Some targeted emergency physicians specifically [35, 36], and others included interprofessional physicians involved in the care of palliative patients with ED visits [37, 38]. The remainder included a more general group of providers and healthcare workers in the ED [39–41], as well as healthcare administrators [42]. Common and informative themes emerged from this collection of studies of healthcare provider attitudes. Among emergency physicians, there is a perceived lack of understanding, lack of training, and discomfort in providing

PC in the ED. The role of the emergency physician was also viewed as more fixed within a culture of stabilization rather than a focus on quality of life. Common themes for emergency physicians included recognition of the complexity of medical decision-making and medicolegal practice concerns in the ED that inhibit consideration of withholding or withdrawing life-sustaining interventions. They also communicated a concern that PC-related questions should have been addressed prior to the ED visit by a primary care provider. In contrast to these findings, a cross-sectional survey of ED residents and faculty reported a high degree of comfort with addressing goals of care and that this skill was within their scope of practice. Specialist PC clinicians in the ED are viewed overall as beneficial for their skills, time, and ability to intervene; but availability is inconsistent, and in some environments specialists are unavailable [35, 36, 43, 44]. Beyond the attitudes of emergency physicians, a broader view from ED-based healthcare providers found similar themes, such as a lack of understanding and a desire for additional training and education, but showed a greater association of PC with end-of-life care than in the physician groups. In addition to medicolegal constraints and a discordant culture of "life-saving" rather than palliation, these studies emphasize the need for greater communication and documentation to prevent undesired outcomes, such as cardiopulmonary resuscitation or intubation in a patient who would not want such interventions [39–41].

Investigations of barriers to care and opportunities for improvement widen the view further, including attitudes of interprofessional clinicians and administrative healthcare professionals, as well as patients and family caregivers. Certain barriers to providing PC in the ED were identified as similar to those seen by ED providers, such as a lack of understanding of PC, a culture of "aggressive care," and medicolegal concerns. PC in the ED was seen as desirable overall and an opportunity for improved patient and family satisfaction, more meaningful care, and decreased costs [37, 38, 42]. When including interviews with patients and family caregivers, in addition to healthcare workers' perceptions of care in the ED, common recommendations for improvement included a need for a more accommodating environment of care, better communication and coordination of care, and greater education and training among ED providers [45–47].

End-of-Life Care in the Emergency Department

Physicians and nurses provide care for the dying and deceased in the ED routinely. As would be expected, studies have demonstrated their support for preserving the dignity of patients dying in the ED, yet they also identified several challenges that threaten their ability to accomplish this goal. Among those challenges are a suboptimal physical environment of care (e.g., little space, limited privacy) and inadequate resources, communications, and coordination of care. Finally, ED provider role ambiguity and insufficient education and training are of concern. Improvement priorities included enhanced communication and symptom management skills, standardized care protocols, adequate space and resources, as well as better ED-PC integration [48–51].

Educational Needs

Two cross-sectional surveys assessed perceived educational needs of emergency medicine residents. The first, published in 2011, surveyed 159 residents at all levels of training from six emergency medicine programs in New York City. Half of those surveyed described having some PC training prior to residency. By the second year of residency, nearly all reported ED experience in managing terminal illnesses and with patients who died. PC was seen as an important competency by 71% of respondents, but only 24% had a "clear idea of the role of PC in emergency medicine." The priorities for additional training included advance directives and medicolegal issues at end of life [52].

The second study from the following year surveyed both residents and faculty from a single program. Approximately half of those surveyed felt they received minimal training in pain management, hospice care, withdrawing/withholding life-sustaining interventions, and management of the dying patient. Similar to the prior study, PC was valued as an important competence by 88% of respondents, and 90% desired more training. Specific topics identified for additional training included discussion of code status and symptom management at end of life. Bedside teaching was the preferred learning modality [53].

Screening

General

The most recent systematic review of triggered PC consults is from 2020 [54]. The authors limited inclusion criteria to prospective quantitative analyses of triggers for consultation for adult patients in the ED and inpatient settings since 2008. All retrospective studies, guidelines, reviews, case reports, editorials, and commentaries were excluded. Overall, three-quarters of the studies were judged to be of moderate to high degree of bias, using the Newcastle-Ottawa scale for nonrandomized studies and the Cochrane risk of bias tool for randomized controlled trials. They concluded that nurses are frequently the primary operators of the trigger tools, and the primary categories focus on advanced illness states and the need for goals of care clarification. Future randomized con-

trolled trials of high quality are still needed to define best practices and to distinguish primary from specialty PC needs. While the ED is included as a primary setting in this systematic review, only one study met their rigorous inclusion criteria. That study, published in 2008 by Mahony et al., demonstrated a low risk of bias [55].

In 2016, previous to the abovementioned systematic review, George et al. published a different systematic review of screening and assessment specific to the ED. Seven studies were included that met their criteria, which included the intervention of "a PC screening tool, assessment, or referral modality aimed at identifying patients appropriate for PC " [56].

The early studies utilize trained professionals within the ED to screen for PC patients with unmet needs. The earliest of these is from 2001. This study created a case finding strategy for at-risk patients ≥65 years old using a triage risk screening tool by the ED nurses, followed by a geriatric assessment tool performed by a geriatric clinical nurse specialist. While not specifically identifying a PC purpose, this study was successful in increasing referrals for supportive services to these elderly patients with unmet needs by sixfold during the 18-month study period and was able to demonstrate modest reductions (2–7%) in repeat ED use at three of four sites within 30 days [57]. Two later studies evaluated unmet PC needs for patients ≥65 years old with the goal of increasing early PC consultation. The first, by Mahony et al. and mentioned in both systematic reviews, used PC nurse practitioners. The second, by Glajchen et al., used a PC social worker. Both studies applied advanced illness criteria with needs assessments to determine which patients would likely benefit from early consultation. In the first study, of 291 patients who had needs assessments completed by the nurse practitioner, 90% were admitted to the hospital, most did not have advance directives, and a median of 68% died within 6 months. Of the deceased, those enrolled in hospice were more likely to die in their place of residence [55]. The second study reported on a group of patients identified by the social worker as having high unmet PC needs and therefore presumed high likelihood of benefit for early PC consultation. Among those recommended for PC consultation in the ED, only half formally received PC consultation, yet 80% died within the 8 months of study enrollment. The biggest reason for not receiving a PC consultation was reluctance on the part of the primary treating physician or the family [58]. Subsequent studies began to integrate the screening process into ED practice.

Speed

In 2011, the Screen for Palliative and End-of-life care needs in the Emergency Department (SPEED) tool was validated as a multidimensional system assessment tool to identify cancer patients on ED arrival who would benefit from PC consultation [59]. This tool was adapted and simplified into a five-question tool (5-SPEED) and integrated into an ED-based palliative intervention program as part of the initial bedside nurse assessment [60].

P-CaRES

In 2015, a broader, yet straightforward tool was developed to identify any patient who might benefit from PC consultation. First, content validity was established using a modified Delphi technique with experts from hospice and palliative medicine [12]. Next, using surveys and case vignettes, the tool demonstrated acceptability and reliability with emergency physicians in the Palliative Care and Rapid Emergency Screening (P-CaRES) project [61]. Finally, the tool was tested among emergency physicians in a convenience sample at a single institution over a 3-week period as an immediate look back on patients from their shift who were ≥65 years old. They found that 32% of patients screened positive for PC consultation, 70% of physicians found the screening tool acceptable to use, and the average time to completion was only 1.8 minutes per patient [62]. Most recently, as part of the Primary Palliative Care for Emergency Medicine (PRIM-ER) project, the P-CaRES tool was adapted into a clinical decision support tool to automate, within the electronic medical record system, the identification of and initiation of services for older adults with unmet PC needs [63].

The Surprise Question (SQ)

The question "would you be surprised if this patient died in the next 12 months?" has shown some utility as a simple tool to predict 1-year mortality. In the ED, the SQ has been used as a possible identifier of patients who might benefit from early PC consultation. In a 2018 study, ED physicians were asked the SQ in a convenience sample of 207 patients ≥65 years old. The SQ alone had a sensitivity of 77% and specificity of 56% in predicting 1-year mortality [64]. Another study included all patients entering through the ED with advanced cancer over a 14-month period. Physicians were asked the SQ retrospectively, and if responding "would not be surprised," they also asked for an estimate of the Eastern Cooperative Oncological Group (ECOG) functional scale. Among 245 patients studied, the median survival was only 3 months. The SQ alone had a sensitivity of 89% in predicting 1-year mortality. The combination of the SQ and ECOG decreased sensitivity to 40% but increased specificity to 92% [65]. The SQ was also used to assess prognostic accuracy in heart failure patients in the

ED and exhibited a sensitivity of 79% and specificity of 57% [66]. Two recent studies adapted the SQ to "would you be surprised if the patient died in one month?" One assessed the prognostic value in all patients ≥65 years old (sensitivity 20%, specificity 93%) [67], and the second assessed its prediction for in-hospital mortality (sensitivity 32%, specificity 85%) [68]. Overall the SQ shows promise as a simple and easily adaptable tool to help in identifying patients with unmet PC needs.

Other ED Screening Projects

Several other trigger-based efforts have been used to identify patients in the ED who would likely benefit from PC consultation. In one, the Functional Assessment Staging (FAST) criteria of >7 was used to identify patients ≥70 years old with advanced dementia and found a disconnect between the predetermined criteria for PC consultation and the ED physician interpretation of appropriateness for consultation [69]. Another used the National Comprehensive Cancer Network (NCCN) guidelines to identify patients with advanced cancer, resulting in earlier PC consultation [70].

Overall, several screening tools appear to be helpful in identifying patients in the ED who may benefit from palliative approaches to care. Challenges remain for efficient integration of PC and in distinguishing primary from specialty-level needs.

Outcomes Research

For the purposes of this discussion, outcomes research refers to ED-initiated PC interventions and patient- and family-reported outcomes, healthcare utilization, and survival. Though studies exist dating from the 1990s, the majority were published in the last 5 years and include several published protocols for ongoing, large multicenter trials [71, 72]. The studies examine the impact of integrated PC models and differing strategies for clinical integration as described by the Improving Palliative Care in Emergency Medicine (IPAL-EM) project from the Center to Advance Palliative Care (CAPC). These include the following models: traditional consult, basic integration, advanced integration, and ED-focused advanced integration [7, 73].

There are two systematic reviews, the first published in 2016 by da Silva Soares et al., followed by Wilson et al. in 2020. The 2016 article considered only studies involving at least one member of a PC team and used hospital admission as their primary outcome. It found insufficient evidence to support the effect of ED-based PC interventions on the outcomes of interest, with the exception of one study suggesting a reduction in hospital length of stay. They urged efforts to provide better evidence in the future through adequately powered and well-conducted randomized controlled trials [74]. The 2020 systematic review reported on the efficacy of ED-based palliative interventions on various outcomes. They noted that the existing evidence was conflicting with marked heterogeneity in design, population, and investigated outcomes, thus limiting a high-level analysis. Nonetheless, they concluded that compared with usual care, ED-initiated PC improves quality of life without decreasing survival time and likely decreases healthcare utilization metrics, such as length of stay [75].

Traditional Model of Consultation

The traditional model of consultation involves contacting a specialist to assist in patient care. Three particular studies show evidence of benefit from PC specialist consultation, focused primarily on the timing of consult. The first, from 2016, found that ED-initiated referral for advanced cancer patients led to earlier symptom control and decreased hospital length of stay compared to referrals initiated while inpatient [76]. A second study, from 2019, looked at adults presenting from long-term care facilities who were triaged as Emergency Severity Index Level 1 (most urgent). They found that formal PC involvement resulted in less aggressive care in 85% of cases; however most of these interventions occurred late in the hospital course with only 9.1% occurring while in the ED. They concluded that this was a missed opportunity to ensure goal-concordant care earlier in the hospital course [77]. A third study from the same year compared the in-hospital mortality of cancer patients directly admitted to the hospital versus those admitted from the ED. The ED patients had a higher overall in-hospital mortality, but PC consults within the first 3 days of admission were associated with decreased mortality when compared to later consultation. This supported a benefit to early PC consultation for ED patients with cancer and urgent-level severity of illness [78].

Basic Integration

Basic integration describes ED and PC programs working collectively to meet objectives with at least some focused initiatives [7]. A randomized controlled trial from a single center in 2016 compared ED-initiated PC consultation to usual care for advanced cancer patients. Quality of life was improved without shortening survival, but with no clear impact on healthcare utilization metrics [79]. Another study from 2016 investigated the feasibility of an educational intervention to identify patients with less than 6 months prognosis. Of the patients identified, 91% of the patients met

hospice eligibility criteria, which succeeded in substantially increasing the number of days enrolled in hospice from baseline [80]. A second feasibility study from 2019 in Singapore tested a care model for metastatic cancer patients. It was designed as a tripartite ED-PC-hospice collaboration, which succeeded in earlier access to PC while, in the ED, including direct admission to a PC unit and to comfort care rooms [81].

Advanced Integration

Studies focused on advanced integration involve targeted screening criteria to identify at-risk patients and a higher level of ED engagement in designing protocols and providing care. The majority of these studies were of cohort design and contained educational interventions to improve general PC skills performed in conjunction with efforts to increase collaboration between emergency and PC providers. In Ireland, Tiernan et al. instituted a four-part intervention including a flagging system for patients known to the service, a screening checklist, education, as well as proactive PC engagement and found patients were 10.5 times more likely to receive a PC consult while in the ED after the intervention with subsequent decreased healthcare utilization [82]. The last study by Weng et al. from Taiwan describes a multi-stage intervention with strong educational components, including an inpatient hospice rotation for the residents, monthly ED interdisciplinary team meetings, and a dedicated cell phone app facilitating communication. This resulted in an increase in DNR orders and hospice consults from the ED [83].

ED-Focused Advanced Integration

Three studies describe ED-focused advanced integration efforts. An organizational level case report by Rosenberg et al. described the institutional development of an ED-based PC team which resulted in increased frequency of DNR orders, improved patient satisfaction, and decreased cost, without impacting the inpatient PC team's consultation volume [84]. A complex multi-step quality improvement initiative by Gruzden et al., the Geriatric Emergency Department Innovations in Care through Workforce, Informatics, and Structural Enhancements (GEDI WISE) model, implemented workforce enhancements, including role redefinition and education of existing providers, and was associated with expedited PC referrals and decreased geriatric ICU admissions from the ED as compared to baseline [85]. Finally, Liberman et al. successfully employed an advanced illness management program, which involved screening by an ED case manager followed by primarily ED-led goals of care conversations and PC available for support. They found an increase in home hospice discharges compared to baseline (39.3% vs 0% respectively) [86].

The remaining outcomes studies focus on improving end-of-life care and communication strategies.

End-of-Life Care

There is, in general, a lack of high-tier evidence regarding best practices for optimization of end-of-life care, specifically for ED patients. Many of the current practice recommendations for emergency care are based on evidence from other settings. A European observational study by Sedillot et al. suggested a five-step protocol for ventilator withdrawal, and two case reports examine end-of-life care transition [87]. A 2013 study by Shlamovitz et al. described improved symptom management after using ketamine for palliative sedation in an ED patient [88]. Wang suggested a systematic approach for comfort care transitions based on an extensive literature review [89]. A descriptive study by Economos et al. evaluated the appropriateness of end-of-life care provided to decedent ED patients based on published guidelines from the French Agency for accreditation and assessment, concluding that the majority of emergency providers recognize when a patient is actively dying and adjust treatments accordingly, with decreased provision of non-beneficial care [90]. Chor et al. described implementation of a protocolized care bundle aimed at reducing variability in the quality of end-of-life care received in a single institution in Singapore. They found that 74% of patients received opioids for pain and dyspnea and over 90% were allowed visitors; however the study lacked comparison data [91]. Finally, a 2020 randomized controlled crossover trial from Thailand compared high-flow nasal cannula to conventional oxygen therapy for relief of dyspnea and hypoxemia respiratory failure and showed significantly decreased dyspnea in the high-flow nasal cannula group compared to conventional therapy [92].

Communication

Best practices for ED-based goals of care conversations remain unclear, but a few studies have provided structure for future consideration. The first, a small Australian study evaluating the implementation of a form designed to guide and document conversations, found that while most physicians supported having the form, recommendations for its ideal format and content varied [93]. A subsequent systematic review found a similar lack of consensus with goals of care conversations in identifying patient candidates, as well as the content and documentation of these conversations [94]. Brief negotiated interview techniques have been successful for other patient care concerns in the ED, and a growing interest

is developing in using these techniques as a structured approach to improve serious illness conversations in the ED [95, 96].

Resource Allocation

In this section, we examine studies describing the interface between emergency care and available internal and external support services. While many studies use decreased ED attendance as a surrogate metric for improved quality of care, we focus here primarily on studies describing collaborative efforts with the ED through improved care coordination or dedicated resources. Organizationally, these studies can be grouped by the timing and location of the resource in relation to the ED visit: (1) community-based care before or after ED attendance, including work done in the field of emergency medical services, or (2) hospital-based resources provided either during ED attendance or after admission. Quality improvement research predominates with most having a descriptive design.

Community-Based

Improved access to community-based PC services can lead to a significant reduction in ED use. In a scoping review of initiatives to reduce inappropriate or non-beneficial hospital admissions at end of life, Taylor et al. note that eight out of ten included studies observe a reduction in ED utilization for patients receiving community-based services [97]. This was also observed by Wiese et al. in a 2008 German cross-sectional study examining emergency calls by cancer patients/families in the last 6 months of life [98]. Similar reductions in patterns of emergency service utilization were found in a 2016 US case control study on the impact of hospice services [99], a 2017 Canadian cohort study comparing palliative intent versus standard homecare nursing [100], and a 2018 Finnish study describing the impact of a growing outpatient PC clinic [101]. This last study also noted improved quality of documented advance care plans in palliative clinic patients.

The first interface for many palliative patients with emergency care is through emergency medical services. Several descriptive studies illustrate the potential benefits of close collaboration between EMS and palliative resources. A case report by Lamba et al. presents four case scenarios highlighting the need for improved collaboration and offers suggestions such as identifying PC champions and creating an action plan via an EMS dashboard [102]. A multicenter German cohort study by Wiese et al. found that emergency providers who were experienced in PC transported significantly fewer patients to the ED [103]. Montgomery et al. describe a quality improvement initiative between EMS and community care providers in Edmonton allowing 61% of calls initiated for symptom crisis to be cared for at home when they would have traditionally required transfer [104]. Two qualitative studies by Kamphausen et al. and Patterson et al. note the impact of resource availability on avoiding unwanted transfer, particularly the importance of up-to-date documentation [105, 106]. There is no conclusive evidence on the best mechanism for communicating care preference across care settings. A small study by McQuown et al. on the transport of DNR orders with patients from extended care facilities found that while 68% of patients had DNR order, only 28% were transferred with the patient and not all of those were recognized by the receiving providers [107]. Lakin et al. found that while emergency physicians perceived advance care planning documents to be very useful, only 31% were very confident they could locate them in the electronic medical record [108]. The most studied method of communicating advance care plans is likely the physician order for life-sustaining treatment (POLST). However, a recent cohort study by Vranas et al. found that the majority of completed POLST forms had no impact on treatment intensity as they were often out of date, were not accessed, or did not indicate a desire for treatment limitations, thus limiting their utility [109].

Within the ED

In many healthcare systems, specialty PC services are a limited resource, and evidence on how to best expand care for emergency patients is also fairly limited. A cohort study by Purdy et al. demonstrated decreased ED attendance and in-hospital deaths after implementing a care initiative including two hospital-based nurses whose role included identifying appropriate patients and facilitating discharge [110]. Lafond et al. described an institutional effort to improve care of terminal ED patients by allocating an ICU comfort care bed to facilitate rapid transfer. This resulted in a reduction in the number of patients dying on stretchers in the ED [111]. A cohort study by Liberman et al. demonstrated reduced 30-day re-visit and admission rates by embedding a specialist care coordinator in the ED who identified patients to be safely discharged with community resources [112].

Due to the events of the COVID-19 pandemic, there has been a surge of renewed interest in allocation of PC resources to include the ED. Several articles describing institutional responses appeared in the literature only months after the pandemic was declared. Chidiac et al. from the UK describe service capacity development by targeted palliative education of the generalist workforce, use of symptom management guidelines, and close partnership with community hospices [113]. The University of Washington's contingency and cri-

sis plan for the ED included an embedded PC specialist for screening and assistance with ED goals of care discussions [114]. Colombia also dedicated a PC team within the ED for early goals of care conversations, noting a reduction in patients desiring full aggressive medical therapy from 82.7% to 18.2% following intervention [115].

After the ED

Gruzden et al. published a protocol for a multicenter randomized control trial comparing the effectiveness of specialty outpatient PC versus nurse-led telephonic palliative care, which will be the first of its kind [116]. Several descriptive studies of bereavement programs show potential benefit. One study from 1999 observed decreased grief intensity in high-risk participants [117]. A more recent study from 2019 noted the positive impact of a bereavement program also on clinicians [118].

Education for Clinicians

Death Disclosure

Early efforts to improve PC skills in the ED focused on the difficult and ubiquitous experience of performing a death disclosure. In 2002, Quest et al. used a structured curriculum for 16 evenly split first- and second-year EM residents to teach and practice death disclosure. The intervention was a combination of large group and small group didactics, followed by a standardized patient (SP) experience. While there was positive feedback and improved comfort with the intervention, the competency assessments of the residents were concordant between faculty and SP, but discordant with the resident self-assessments. Resident self-assessments of competency tended to be higher than faculty or SP assessment [119]. The same assessment tool, identified as the affective competency score (ACS), was later used to evaluate fourth year medical students rotating in the ED. It again demonstrated concordance with faculty and SP, but similar discordance with student self-assessment. Together, these findings support the use of the ACS as a valid and reliable tool for faculty and SPs to assess death disclosure [120].

A similar approach using the aptly named GRIEV_ING mnemonic was studied first with residents, then with paramedics. In the first study, 20 residents received a 2-hour educational session, including small group, role-play, and a didactic lecture. The residents were followed to assess retention after 3 months. Assessments of self-confidence and competency (by a trained SP and blinded audio rater, with high inter-rater reliability) improved from before and after the intervention with stability over time [121]. The GRIEV-ING mnemonic was later studied with 30 paramedics, limiting assessments to pre-/post-intervention, and found again an increase in self-confidence and competency (assessed by a trained SP) [122].

EPEC-EM

The Education in Palliative and End-of-life Care for Emergency Medicine (EPEC-EM) project is a comprehensive curriculum designed to facilitate teaching primary PC skills to EM clinicians. In 2010, Gisondi et al. published an adaptation of the curriculum for EM residents at a single academic medical center. The 14 curricular modules were divided into equal parts of synchronous (lectures) and asynchronous (electronic media) teaching strategies and demonstrated similar knowledge transfer, supporting selectively flexible approaches to delivering the curriculum [123]. The same year, Ponce et al. demonstrated improved comfort with prehospital personnel in a pilot study using the EPEC-EM modules as a training method for death disclosure and family-witnessed resuscitation [124]. A later study used selective topics from EPEC-EM to study the effect of EM resident behaviors and retention of information over a 6-month period after a brief educational intervention (4 hours of didactic learning in a single day). Based on comparison survey results, residents did not retain information on opioid conversions and dyspnea in the dying patient but retained knowledge of hospice qualifying diagnoses. This resulted in an observed 88% increase in direct ED to hospice referrals during the study period [125]. A more recent study used a simulation-based intervention focusing on rapid assessment of PC patients in the ED, derived from an EPEC-EM module. Residents demonstrated an increase in both the perceived importance of primary PC skills for EM physicians and self-reported confidence in using these skills [126]. In both of these last two studies, time limitations were identified as possible barriers to clinical implementation.

Training Efforts

Taking a broad view of how EM training programs in the United States incorporate PC principles, Kraus et al. surveyed the leadership from over 100 programs, representing 6 states where fully half of residency programs are located. They published in 2016 that a slight majority of EM programs taught PC skills. The following factors were associated with PC teaching: familiarity with EPEC-EM, HPM consult availability in the ED, and access to an HPM rotation. The topics of greatest importance were crucial conversations, pain management, and care of the imminently dying. The most effective teaching methods were

bedside teaching, HPM faculty mentorship, and case-based simulation. An interesting disconnect was noted between senior resident self-perception of competence and the following topics: the dying child, withdrawing and withholding life-sustaining treatments, and ethical and legal considerations of care. Faculty and resident barriers to implementation of the curriculum included a lack of subject expertise and a lack of interest [127]. By comparison, a Canadian study surveyed 26 programs (out of 36) and found that a minority of programs had any structured curriculum in PC. Of those, 100% were lecture or seminar-based approaches. Half had an elective rotation in HPM available, but only one had a mandatory rotation. Identified barriers to the incorporation of PC skills into the curriculum included lack of time and concerns of assuring that the content was relevant and current [128].

Two additional efforts deserve mention. The first used experts from HPM and EM to define content areas and competencies for primary PC skills and applied their recommendations to the EM Milestones for residency training [129]. The second provides the protocol of an expansive project currently underway looking at the impact of a comprehensive program of education and skills in primary PC for ED providers: the Primary Palliative Care for Emergency Medicine (PRIM-ER). This project will lead to a randomized controlled study of the effect of their interventions in 33 EDs across the country [71].

Summary

In this chapter, we have presented an overview of the rapidly growing research addressing the interface of PC within the ED. For structure, we relied on guidance from a 2011 workgroup of experts from both fields who created six priorities for research efforts: descriptive, attitudinal, screening, outcomes, resource allocation, and education for clinicians. Further categorization used study descriptions from the methodology sections for each referenced article (see Table 63.1). While a true analysis of the hierarchy of evidence was beyond the scope of this chapter, recent robust and well-powered study designs show promise in the emerging literature to guide future best practices in the ED care of patients with serious illness.

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Part VI

Contextual

Ethics

64

Kenneth V. Iserson

Introduction

Bioethical issues often arise when treating emergency department (ED) and prehospital care patients. Actual or anticipated bioethical dilemmas commonly occur among patients with hematologic and oncologic diseases, and these dilemmas may require slightly different approaches than in other ED patients due to attitudes toward and the nature of the disease processes. Bioethical dilemmas raised by emergency hematologic-oncologic patients fall into four categories (Table 64.1): decision-making, treatment demands and refusals, system problems, and notifications.

Bioethics can be a nebulous concept, so the first order of business will be to lay the groundwork by describing bioethics and discussing how it fits into our societal and professional value systems. Then, I will briefly review basic ethical (foundational) theories and the methods used to think through ethical dilemmas, followed by a discussion of the mid-level ethical principles with which clinicians may be more familiar. While they may appear superficial or oversimplified, these mid-level principles provide an easy way to think about the issues posed in bioethical dilemmas and policy development. Therefore, when treating emergency patients with hematologic and oncologic illnesses, we use them to convey common moral themes, such as decision-making, demands for and refusals of treatment, and system constraints. Finally, I will move into the area of virtues to discuss notifications to patients and survivors.

Table 64.1 Categories of bioethical issues encountered when working with patients with hematologic-oncologic diseases and their families

Decision-making (*autonomy*)
1. Dying. Surrogates and advance directives (living will, medical power of attorney, prehospital advance directives)
2. Decision-making capacity
Treatment demands/refusals (*beneficence, nonmaleficence*)
1. Demands to "do everything"
2. Palliative care decisions (demand to do "nothing"—Comfort care only)
3. Refusal of analgesics
4. Refusal of possibly beneficial treatment (including decisions based on religious beliefs)
System dilemmas (*distributive justice, confidentiality*)
1. System problems (inability to pay, intentional/unintentional release of patient information, undocumented alien, "wrong" insurance or medical system/group)
2. Collegial problems (refusal to see patient, abandonment, etc.)
3. Research protocols
Notification (*honesty with sensitivity*)
1. Notifying patient/family of diagnosis
2. Notifying survivors of death

How Bioethics Fits into Our Societal and Professional Value Systems

Bioethics, or clinical ethics, describes how we apply professional and societal values in an organized way to find reasoned and defensible solutions for moral dilemmas. Moral dilemmas are those situations in which an individual must make a decision between conflicting or competing values. The resolutions to such dilemmas, however, do not always hinge on determining right versus wrong or good versus evil. Rather, moral dilemmas more often deal with "gray areas," where the situations or resolutions initially seem to be equivalent, i.e., situations with seemingly equal merit or apparently equal injury. In these more ambiguous situations, we use ethical values to help determine a morally acceptable course of action.

In a pluralistic society, we derive these values from a variety of sources, including the general cultural, philosophical, and religious moral traditions, the social norms embodied in law, and our professional oaths and ethical codes. Each of these sources claims moral superiority. The goal of bioethics is to help us understand, interpret, and weigh these competing moral values [1].

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Case Study 1

The following case represents an example of how bioethics can be applied when a cancer patient presents to the ED.

An exsanguinating adult leukemic patient, awake and still with medical decision-making capacity, arrives in the ED and explicitly states that, owing to long-standing religious beliefs, she wants no blood or blood products. The physician, with a professional duty and moral commitment to preserve life, does not personally agree with the patient's decision. Yet, society (through the benchmark of court decisions) has repeatedly sided with the patient's right to refuse such treatment.

In this case, the patient's autonomy and right to practice her religion are recognized as the overriding values. The case becomes somewhat less clear when the patient lacks decision-making capacity, is a minor, or appears to be under external pressures (such as from relatives) to make what is a life-threatening decision. In my experience, however, when clinicians truthfully tell patients that they will die quickly without the transfusion, most consent. Some clinicians, steeped in the idea of patient autonomy, forget that informed consent includes informing the patient of all the relevant benefits and risks—including death.

Values in Emergency Medicine

Values describe the standards that individuals, institutions, professions, and societies use to judge human behavior. We learn values, usually at an early age, through indoctrination into the birth culture, from observing behavior, and through secular (including professional) and religious education. They are moral rules derived from ethical principles that promote those things we think of as good and minimize or avoid those things we think of as bad. Societal institutions incorporate and promulgate values, often attempting to retain old values even in a changing society.

In pluralistic societies, clinicians must be sensitive to alternative beliefs and traditions, since they treat people with multiple and differing value systems. Not only religious but also family, cultural, and other values contribute to patients' decisions about their medical care; without asking the patient, there is no way to know what decision they will make [2].

Although many people cannot answer the question "What are your values?", physicians can get concrete expressions of patients' uncoerced values by asking what they see as their goal of medical therapy and why they want specific interventions. In patients who are too young or who are deemed incompetent to express their values, physicians may need either to make general assumptions about what a normal person would want done or to rely on surrogate decision-makers [2].

Institutions, including healthcare facilities and professional organizations, have their own value systems. Healthcare facilities often have specific value-related missions. Religiously oriented or affiliated institutions may be the most obvious of these, but charitable, for-profit, and academic institutions also have specific role-related values. Professional organizations' values often appear in their ethical codes [3].

Clinicians also have their own ethical values, based on religious, philosophical, or professional convictions. While conscience clauses permit clinicians to "opt out" when they feel that they have a moral conflict with professionally, institutionally, or legally required actions, they are generally required to provide timely and adequate medical care for the patient—which may be particularly difficult to achieve in emergency medicine [3].

Virtues in Emergency Medicine

Virtues describe admirable personal behavior that Aristotle and other philosophers claim is derived from natural internal tendencies [4]. The virtuous person concept can be summed up with the ancient saying: "In a place where there are no men, strive to be a man!" [5]. Virtuous behavior stems from a sense of duty and the perception that it is the right thing to do, rather than from a desire to garner personal benefits. These ideal, morally praiseworthy character traits (e.g., showing kindness) are evident across many situations throughout the person's lifetime. Virtues that may be inherent in emergency medicine clinicians include courage, safety, impartiality, personal integrity, trustworthiness, and fidelity [1].

Courage allows one to fulfill an obligation despite reasonable personal risk. The courageous clinician also advocates for patients against incompetent practitioners and those who attempt to deny them care, autonomy, or confidentiality. *Safety* balances unreasoned courage. *Impartiality* prompts the emergency physician (EP) to provide unbiased, unprejudiced, and equitable treatment to all patients, without regard to their race, creeds, customs, habits, or lifestyle preferences. *Personal integrity* incorporates *trustworthiness*, which prompts clinicians to protect their sick and, often, vulnerable emergency patients' interests by exercising ethical principles. *Truth telling* (fidelity, honesty) prompts clinicians to provide patients with the known facts, but tempered with humility and sensitivity.

Bioethics, Religion, and Law

Religion Organized religions have long been recognized as the guardians of a society's values. Religious values have therefore been an important component of ethical deliberations in medicine, as elsewhere in society. Modern secular bioethics incorporates many religion-originated decision-making methods, arguments, and ideals [6]. Although various religions may appear to be dissimilar, most have as a basic tenet (no matter how it is stated) the Golden Rule: "Do unto others as you would have them do unto you." Religious values are important from two perspectives: the patient's in the exercise of autonomy and the practitioner's in placing limitations on what he or she can morally do. Given the overwhelming importance of patient autonomy in modern Western bioethics and law, however, a practitioner's religious convictions can only guide his or her actions. If their values differ, clinicians must follow the patient's wishes, as long as they are legal and practicable, and they do not violate medicine's basic ethical precepts.

Law Laws are rules of conduct established by legislatures, administrative agencies, courts, or other governing bodies. They often vary from locale to locale and are enforceable only in the jurisdiction where they prevail. Law and bioethics both provide rules of conduct to follow based on societal values. But, while good ethics often makes good law, good law does not necessarily make good ethics [6].

So, how does bioethics differ from law? The law, unlike bioethics, is relatively rigid and, particularly in the case of scientific and medical issues, can lag years or even decades behind modern developments. Societal values are incorporated both within the law and within ethical principles and decisions. By contrast, ethics is more inclusive within a culture, incorporating the broad values and beliefs of correct conduct. The primary differences between law and bioethics are shown in Table 64.2 [3].

Table 64.2 Relationship between the law and bioethics

Bioethics	Function	Law
✓	Case-based (casuistic)	✓
✓	Existed from ancient times	✓
✓	Changes over time	✓
✓	Strives for consistency	✓
✓	Incorporates societal values	✓
✓	Basis for healthcare policies	✓
	Some unchangeable directives	✓
	Formal rules for process	✓
	Adversarial	✓
✓	Relies heavily on individual values	
✓	Interpretable by medical personnel	
✓	Ability to respond relatively rapidly to changing environment	

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Emergency physicians often look to the law for answers to thorny dilemmas. Yet, except for the rare cases of "black-letter law" wherein very specific actions are mandated, clinicians can best resolve these issues by turning to bioethical reasoning, using bioethics consultations, or applying previously developed institutional bioethics policies.

Modern bioethics developed because the law often has remained silent or inconsistent on matters vital to the biomedical community. The rapid increase in biotechnology, the failure of both the legal system and legislatures to deal with new and pressing issues, and the increasing liability crisis drove the medical community to seek answers to the difficult questions that practitioners have to work through on a daily basis [3].

Oaths/Codes

Medical ethics, or bioethics, differs from ethics in other fields just as medicine differs from other professions. This is because physicians treat ill people who are dependent on them and vulnerable to exploitation. For this reason, physicians have used ethical codes since ancient times to guide their behavior. Modern physicians who deliver critical hematologic and oncologic emergency medical services still rely on this guidance to help resolve dilemmas.

Many healthcare professional organizations, including most involved with emergency care, have developed their own values statements, which they often incorporate into their ethical codes. These codes (and the associated oaths) promote moral standards that their members presumably agree with and are expected to follow. The interpretation of those principles often evolves, albeit sometimes slowly, as the larger society changes. For example, although the American Medical Association's Code of Ethics was first published in 1847, it was not until 2001 that it stated that the physician's primary responsibility should be to their patient. While existing medical professional codes differ markedly (Table 64.3), all try to provide a "bottom line"—that is, a minimally acceptable course of action [2].

Some professional oaths and codes conflate bioethics and professional etiquette. However, these two areas differ markedly: professional etiquette deals with standards governing the relationships and interactions between practitioners, while bioethics is concerned with basic moral values and patient-centered issues [7]. Specifically, bioethics deals with relationships between providers and their patients, providers and society, and society and patients.

Review of Basic Ethical (Foundational) Theories

Foundational ethical theories embody grand philosophical ideas that attempt to coherently and systematically answer two

Table 64.3 Comparison of the ethical precepts contained in the Hippocratic Oath and five ethical codes used by emergency medicine professional organizations

Principle or concept	Society for Academic Emergency Medicine	American College of Emergency Physicians	Emergency Medicine Residents' Association	American Medical Association	American Osteopathic Association (adopted by the American College of Osteopathic Emergency Physicians)	Hippocratic Oath
Protect patient confidentiality		X	X	X	X	X
Maintain professional expertise	X	X	X	X	X	X
Committed to serve humanity	X	X	X	X	X	
Patient welfare primary concern	X	X	X	X		X
Considerate to patients, colleagues	X	X	X	X		X
Respect human dignity	X	X	X	X	X	X
Safeguard public health	X	X	X	X		X
Protect vulnerable populations	X	X	X	X	X	X
Advance professional ideals	X	X	X	X	X	X
Honesty		X	X	X	X	
Report incompetent, dishonest, impaired physicians		X	X	X		
Moral sensitivity	X	X		X		
Obtain necessary consultation				X	X	X
Altruism in teaching	X					
Fairness to students, colleagues				X		X
Obey, respect the law			X	X	X	
Prudent resource use	X	X	X			
Work to change laws for patient benefit			X	X		
Not abuse position or privileges, including sexual harassment	X				X	X
Respect for students	X					X
Choose whom to serve except in emergencies				X	X	
Follow research guidelines	X				X	
No abortions						X
No euthanasia						X
Do not compromise clinical judgment for money					X	
Universal access to healthcare				X		
Preserve human life						X

American College of Emergency Physicians (ACEP). Code of Ethics for Emergency Physicians. Revised Jan 2017. www.acep.org/patient-care/policy-statements/code-of-ethics-for-emergency-physicians/. Accessed 22 Sep 2019; Emergency Medicine Residents' Association (EMRA). Code of Ethics for Emergency Physicians. Revised Jun 2019; American Medical Association (AMA). AMA Code of Medical Ethics, Revised Jun 2001; American Osteopathic Association (AOA/AOCEP). The AOA's Code of Ethics. Updated 24 Jul 2016. https://osteopathic.org/about/leadership/aoa.governance-documents/code -of-ethics/. Accessed 22 Sep 2019; Hippocratic Oath. Miles [37]

fundamental questions: What ought I do? How ought I live? Philosophers continue to elaborate or reconstruct fundamental ethical theories based on ancient ethical systems. Many were developed in India and China or within the Jewish, Christian, Islamic, and Buddhist religions. Clinicians generally have difficulty directly applying these theories to individual situations. Rather, they rely on "casuistry," a case-based application of bioethical values (described later in this chapter).

There are two main "foundational" theories of ethics: utilitarianism and deontology.

Utilitarianism, sometimes called consequentialism or teleology, is one of the more functional and commonly used ethical theories. Based on writings by John Stuart Mill and Jeremy Bentham, it focuses on getting good or valued results rather than using the right means to achieve those results. This theory promotes achieving outcomes that benefit the majority in the most impartial way possible. In its simplest form, this theory proposes achieving the greatest good (or the greatest sum of pleasure or the least amount of pain) for the greatest number of people. It is often advocated as the basis for broad social policies. Health planners often employ concepts of utility to develop more equitable health delivery systems. Such systems attempt to encourage and maximize the use of treatment that results in the most beneficial outcome for the least resource expenditure. Nevertheless, trying to define what is "good" or who comprises the affected community exposes the major problems with this theory [8].

Utilitarian principles apply to ED triage systems that regulate the resources given to each patient to maximize overall benefit. However, physicians should not use the utility concept as an excuse to deny an individual patient needed and available resources merely to add to society's greater good. In doing this, the physician would be abandoning the traditional healer's role and violating the bioethical principle of beneficence.

Deontology (rule-based ethics) is based on moral absolutes—something is either right or wrong. Adherents hold that certain unbreakable moral rules govern the most important aspects of our lives, even if following the rule leads to results that may not be "good." One example of a list of "unbreakable" rules is the Ten Commandments. The philosopher Immanuel Kant is often identified with this theory.

However, major problems can arise in applying rule-based ethics. The first is that moral rules may vary depending on one's culture or subculture. This can lead to great divisiveness over the interpretation of what might seem, at first glance, to be an obvious and straightforward rule. For example, does the common stricture "Do not kill" prohibit passive euthanasia (allowing death without intervening) or physician-assisted suicide (providing a patient with a lethal medication prescription)? The rigidity inherent in rule-based ethics causes difficulties when confronted with real-life situations. For some individuals, however, such a system provides necessary guidelines on how to conduct oneself in life.

Other commonly cited ethical theories include:

Natural Law

This system, often attributed to Aristotle, suggests that man should live life according to his inherent human nature, in contrast to man-made or judicial law. Natural law is often associated with particular religious beliefs, especially Catholicism. The claim that the medical profession has an inherent morality mirrors natural law.

Virtue Theory

This theory asks what a "good person" would do in specific real-life situations. It stems from the writings of Aristotle, Plato, and Thomas Aquinas in which they discuss such timeless and cross-cultural character traits as courage, temperance, wisdom, justice, faith, and charity. The Society for Academic Emergency Medicine adopted a virtue-based Code of Conduct.

Mid-Level Ethical Principles

"Mid-level principles" that guide clinical practice and bioethical thought are derived from ethical theories, but are more specific and less abstract. Instead, these ethical principles are "action-guides," basically, role-specific duties that physicians owe to patients, consisting of various "moral rules" that comprise a society's values [9].

By melding medicine's goals with societal morality, law, religious values, and societal expectations for the profession, Beauchamp and Childress popularized the most commonly cited mid-level principles: autonomy, beneficence, nonmaleficence, and distributive justice. These four principles provide a handy medical ethics template and a practical, although often difficult to apply, checklist to use when considering the moral implications of specific cases [8, 9].

A question that naturally arises is whether ethical principles are universal. For individual clinicians, the bioethical principles they follow, and the values that stem from them, do not change because of geography. Clinicians practicing or teaching within cultures other than their own have a responsibility to continue applying their core ethical principles while being sensitive to the local population's values [10].

I will discuss autonomy in more depth (below), since it directly affects many decisions and ethical dilemmas that emergency clinicians face when caring for patients with hematologic-oncologic problems. These include whether a patient has the capacity to make his or her own decisions, who can act as surrogate decision-makers, and what is the role of advance directives. The other principles—and virtues—will be discussed in relationship to specific ethical dilemmas, such as demanding and refusing treatment, constraints imposed by healthcare systems, and patient/survivor notifications.

Decision-Making Capacity

Autonomy means, as Justice Cardozo said, "Every human being of adult years and sound mind has a right to determine what shall be done with his own body" [11]. Physician adoption of patient autonomy has been a major change from the millennia-old tradition of medical paternalism (or parentalism), that is, doing what the physician thinks is good for the patient regardless of what the patient desires. Grounded in the moral principle of respect for persons, autonomy recognizes the right of adults with decision-making capacity to accept or reject recommended healthcare interventions, even to the extent of refusing potentially lifesaving care. Physicians have a concomitant duty to respect their choices. Over the past several decades, autonomy has become the predominant value in US medicine and society, although paternalism is still the prevailing attitude in most of the world.

One important, and often misunderstood, aspect of autonomy is that individuals who retain decision-making capacity can voluntarily and verbally assign decision-making authority to other people (e.g., family) for a specific decision or time period, such as when they are in the emergency department. Since patients may exercise their autonomy only if they have decision-making capacity, emergency clinicians must be able to determine this at the bedside so that if necessary, surrogate decision-makers may become involved.

While autonomy has become ingrained in US medical professionals, clinicians need to be sensitive to *communitarianism,* which is a counterbalance to autonomy. Communitarianism considers the larger picture of the patient's life, including his or her family and community, when puzzling through a bioethics case or developing public policy. This principle generally holds that the community's welfare outweighs an individual's rights or good and thus requires that deliberations involve communal (e.g., family, elders) discussions [8]. Many cultures rely on communitarian deliberations when making medical choices and use this pattern for public policy decisions. When making bedside ethical decisions, physicians should determine, whenever possible, not only their patient's individual values but also whether the patient subscribes to an individualistic or a communitarian ethic [6].

Evaluating Decision-Making Capacity

Many ethical dilemmas in emergency medical care revolve around ascertaining a patient's decision-making capacity. In clinical settings, the question of decisional capacity is most often linked with consent to (or, more often, refusal of) a medical procedure.

Capacity refers to a patient's decision-making ability that, in the ED, EPs determine at the bedside rather than by the courts, a psychiatrist, or a lawyer. ("Competence" is a legal term and can only be determined by the court.) Decisional capacity is always related to the type of decision involved, although it is unclear whether it should be based on the potential seriousness or irreversibility of the outcome of a patient's decision (e.g., refusing lifesaving intubation) or on the complexity of the information needed to make the decision (e.g., whether to enter an experimental cancer treatment protocol). In current practice, most clinicians and ethicists use the seriousness or irreversibility of the outcome as the key to determining decisional capacity.

Table 64.4 Components of decision-making capacity

1. Knowledge of the options
2. Awareness of consequences of each option
3. Appreciation of personal costs and benefits of options in relation to relatively stable values and preferences

From Buchanan [38]. © 1995 by Galen Press, Ltd. All rights reserved. Used with permission of Galen Press, Ltd., Tucson, AZ

To have adequate decision-making capacity in any circumstance, an individual must understand (a) the options, (b) the consequences of acting on the various options, and (c) the personal costs and benefits of these consequences related to a relatively stable framework of personal values and priorities (Table 64.4) [12]. Assessing this last criterion can be especially difficult when clinicians have poor verbal skills in the patient's language. An easier, albeit incomplete, method of assessing this criterion is to ask the patient "why" a particular decision was made. This often provides an approximation of the last (and most important) criterion for assessing decisional capacity.

Disagreement with the physician's recommendation is not in itself grounds for determining that the patient is incapable of making his own decisions. In fact, even refusal of lifesaving medical care may not prove that the person is incapable of making valid decisions if he or she makes it on the basis of firmly held religious beliefs, as when a Jehovah's Witness patient refuses a blood transfusion.

Patient Consent

If a patient has decision-making capacity, a clinician who respects a patient's autonomy must get the patient's consent for any intervention. The consent need not be associated with a formal document, although an appropriate level of explanation is always required.

There are three general types of consent: presumed, implied, and informed. Presumed consent, sometimes called emergency consent, covers the necessary lifesaving procedures that reasonable people would usually wish to have performed on them. *Presumed consent* conjoins a patient's "best interest" with physician beneficence. Stopping hemorrhage and securing an airway in an unconscious, unknown patient

are common examples of procedures performed under this type of consent. *Implied consent* occurs when a patient with decision-making capacity simply cooperates with a procedure, such as holding out their arm to give blood or to allow placement of an intravenous line. Indeed, this is the most common type of consent in medical practice [13].

Informed consent occurs when a patient who retains decision-making capacity is given all the pertinent facts regarding a particular procedure's risks and benefits, understands them, and voluntarily agrees to undergo the procedure. The requirement for informed consent varies in practice and law from area to area and even among practitioners and institutions in the same area. If a patient lacks decision-making capacity, get a surrogate decision-maker involved.

Advance Directives and Surrogate Decision-Makers

Advance directives loosely include durable powers of attorney for healthcare, living wills, prehospital advance directives [14], and similar documents initiated or approved by physicians, such as prehospital DNAR, inpatient DNAR forms, and Physician Orders for Life-Sustaining Treatment (POLST). They do not, however, include nonstandard and indecipherable directives [15–17]. The standard and generally recognized documents often express the patient's autonomous wishes about the treatment he or she will receive. However, they only go into effect if the patient lacks decision-making capacity. Otherwise, ask the patient what he or she wants done.

When patients do not have the capacity to make medical decisions for themselves, someone must make the decision for them. Four major classes of decision-makers have been proposed, and actually used, in these situations: family, bioethics committees, physicians, and courts.

Traditionally, and usually in practice, the family, especially the spouse, makes medical decisions when a patient does not have decision-making capacity. A typical prioritization list of those empowered to act as surrogate decision-makers is often stipulated in state statutes, similar to Arizona's landmark law (Table 64.5) or in a hospital's policy. When no surrogates exist, all potential surrogates refuse to act in that capacity, or an irresolvable conflict exists between surrogates at the same level (such as siblings), the court will intervene.

Surrogates make decisions in one of two ways. The first is *substituted judgment*, which is used when the surrogate is not certain what the patient would want done in a particular situation. Substituted judgment attempts to determine and act in accordance with the patient's values based on the patient's prior statements and behavior, without advance directives or other explicit direction. This is the most worrisome type of surrogate decision-making, because it is based on the most ambiguous grounds. The second way, or *best interest* standard, is used when the patient has never had adequate decision-making capacity, and the surrogate must simply act in the patient's best interest. Unless there is already a court-appointed guardian, these cases often end up being resolved in a courtroom.

Table 64.5 Statutory surrogate decision-maker list: an example

Arizona Revised Statute: Living Wills and Health Care Directives Act, Title 36, Chap 32. 1992. Revised 2005
1. The patient's *spouse*, unless the patient and spouse are legally separated
2. An *adult child* of the patient. If the patient has more than one adult child, the healthcare provider shall seek the consent of a majority of the adult children who are reasonably available for consultation
3. A *parent* of the patient
4. If the patient is unmarried, the patient's *domestic partner* if no other person has assumed any financial responsibility for the patient
5. A *brother or sister* of the patient
6. A *close friend* of the patient. For the purposes of this paragraph, "close friend" means an adult who has exhibited special care and concern for the patient, who is familiar with the patient's healthcare views and desires, and who is willing and able to become involved in the patient's healthcare and to act in the patient's best interest
7. If the healthcare provider cannot locate any of the people listed [above], the patient's *attending physician* may make healthcare treatment decisions for the patient after the physician consults with and obtains the recommendations of an *institutional ethics committee*. If this is not possible, the physician may make these decisions after consulting with a second physician who concurs with the physician's decision. For the purposes of this subsection, "institutional ethics committee" means a standing committee of a licensed healthcare institution appointed or elected to render advice concerning ethical issues involving medical treatment

Children pose a special situation. Individuals less than the age of majority (and unemancipated) are usually deemed incapable of making medical decisions for themselves, although clinicians normally explain the situation to the child and ask for his or her assent. In most cases, the same rules for decision-making capacity that apply to adults also apply to children. The more serious the consequences, the more important it is that the child understands the options and consequences and can articulate the values involved in making their decision. Especially in cases involving religiously or culturally based refusal of potentially lifesaving treatment or when the parents disagree, the court or child protective services may intervene on the child's behalf.

Methods of Applying Bioethics Principles

To apply bioethical principles to a clinical situation, one first must recognize that a bioethical dilemma exists, which is not always an easy task. Once identified, addressing the problem brings its own challenges. Clinicians adhere not only to basic bioethical principles but also, at least tacitly, to a number of

professional, religious, and social organizations' ethical oaths, codes, and statements. This complexity can produce a confusing array of potentially conflicting bioethical imperatives.

When dealing with bioethics cases, clinicians need to use ethical reasoning, which includes the application of foundational theories, mid-level principles, and case-based reasoning. This helps us systematically identify elements within moral problems that we otherwise might overlook.

Casuistry, or case-based ethics, attempts to define problems and correct courses of action based on the intricacies of a particular case. It puts an emphasis on what Aristotle called *phronesis*, or "practical wisdom," and is the basis for the emergency rapid decision-making model, described below. To use this method, examine each case for its similarities and differences with select previous cases paradigms, for which you have determined a suitable course of action. Where the present case is similar enough to the paradigm, use the same course of action. When significant differences exist, clinicians must apply the broader mid-level principles derived from rule-based, utilitarian, and other ethical systems, usually giving the most weight to patients' autonomy and values.

In practice it can be difficult to identify and extract the most appropriate and useful principles to apply to a particular case. Some principles may appear too vague, or perhaps several conflicting principles appear to apply to a given case. The key is to prepare for bioethical problems as one would for critical medical events, by reading about, reflecting on, and discussing how to approach these issues. This leads not only to increased personal preparation but also to more general policies that provide guidance for dealing with difficult bioethical issues [2].

Prioritizing Conflicting Principles: The Bioethical Dilemma

Applying bioethical principles can be confusing. When two or more seemingly equivalent principles or values appear to compel the clinician to act in different ways, a bioethical dilemma exists. This situation is often described as being "damned if you do and damned if you don't," where any potential action appears, on first reflection, to be an option between two seemingly equivalent "goods" or "evils." In bioethics, although there may be disagreements regarding the optimal course of action using a specific set of values, there is often general agreement as to what constitutes ethically wrong actions. While we theoretically have a duty to uphold each bioethical principle, none routinely "trumps" another.

Working through bioethical dilemmas generally requires a case-based approach. The key is to use paradigm and analogy (the first step in the rapid decision-making model, described below). Thus, when faced with a troubling case, first identify relevant mid-level principles and alternative courses of action. Then, compare it to similar but much clearer paradigms, that is, cases having resolutions with which virtually any "reasonable person" will agree. Identifying such cases may be difficult; it takes experience and a significant knowledge base. Using bioethics committees and bioethical or legal case databases may help.

Application to Emergency Medicine: The Rapid Decision-Making Model [18, 19]

When faced with bioethical dilemmas, emergency clinicians often must make ethical decisions with little time for reflection or consultation. Ethical problems, like clinical problems, require action for resolution. For that reason, a rapid decision-making model was developed, based on accepted bioethical theories and techniques (Fig. 64.1). It provides guidance for emergency medicine practitioners who are under severe time pressures and wish to make ethically appropriate decisions [18, 19].

When using this approach, the clinician must first ask: "Is this an instance of a type of ethical problem for which I have already worked out a rule?" Or, at least, is it similar enough to such cases that the rule could be reasonably extended to cover it? In other words, if there had been time in the past to think coolly about the issues, read about them, discuss them with colleagues, and develop some rough guidelines, could they be used in this case? Just as with the indications for any clinical emergency procedure, EPs should be prepared with a course of action for at least the most common ethical dilemmas likely to occur in the ED. If the case in question does fit under one of those guidelines arrived at through critical reflection, and there is not time to further analyze the situation, then the most reasonable step would be to follow that rule—if it is still appropriate. In ethics, this step follows from casuistry or case-based reasoning.

If the case does not fit under any previously generated ethical rule, the practitioner should consider if there is an option that will buy time for deliberation. If there is such an option, and it does not involve unacceptable patient risks, then it would be the reasonable course to take. Using a delaying tactic may afford time to consult with other professionals, the bioethics committee, and the family.

If there is no acceptable delaying tactic, the clinician should weigh what she considers the best option using a set of three tests, drawn from three different philosophical theories, to help make a decision:

Impartiality Test "Would you be willing to have this action performed if you were in the other person's (the patient's) place?" A version of the Golden Rule, it helps correct one obvious source of moral error—partiality or self-interested bias.

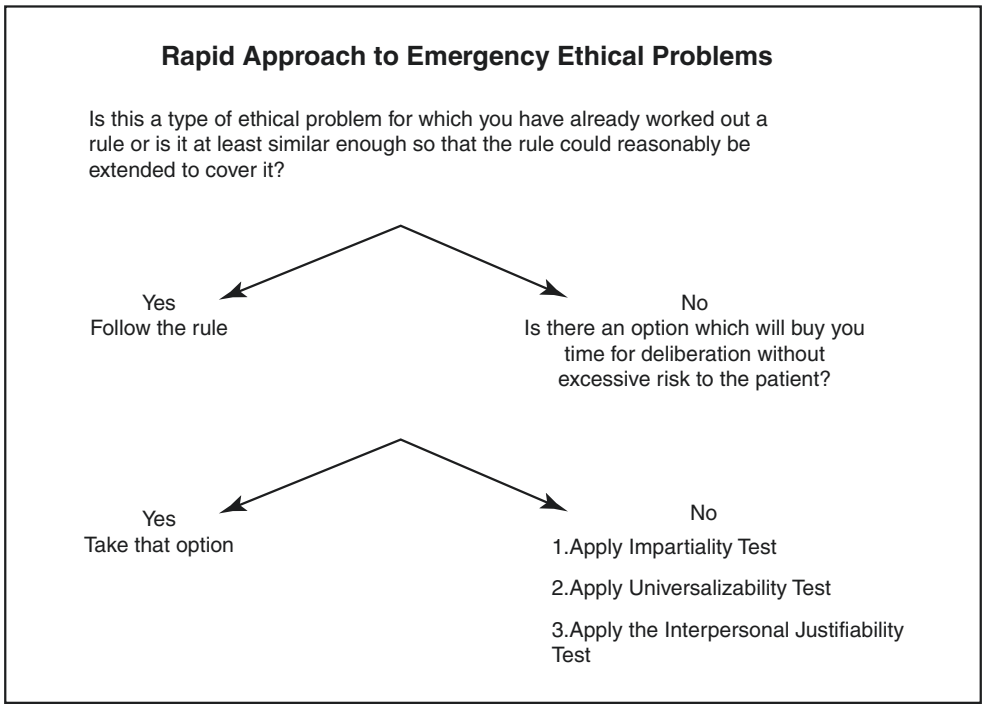

Fig. 64.1 Rapid decision-making model. (From Iserson [39], Figure 2, pg 45. © 1995 by Galen Press, Ltd. All rights reserved. Used with permission of Galen Press, Ltd., Tucson, AZ)

Universalizability Test "Would you be comfortable if all clinicians with your background and in the same circumstances act as you are proposing to do?" This generalizes the action and asks whether developing a universal rule for the contemplated behavior is reasonable—an application of Kant's categorical imperative. This helps eliminate not only bias and partiality but also short-sightedness.

Interpersonal Justifiability Test "Can you give reasons that you would be willing to state publicly? Will peers, superiors, or the public be satisfied with the answers?" This uses a theory of consensus values as a final screen.

When ethical situations arise in cases for which no time exists for further deliberation, it is probably best to go ahead and act on the previously determined ethical rule or take the course of action for which the clinician was able to answer all three tests in the affirmative with some degree of confidence. Once the crisis has subsided, clinicians can hone their ethical decision-making abilities by reviewing the decision with colleagues and bioethicists. As an example:

Case Study 2

An elderly man arrives at the ED with a diminished state of consciousness and a diminished respiratory rate. The EMS personnel who are bagging him say that they were told that he has "cancer," but had no additional information. No one accompanied him. Upon removing his shirt, they find "Do Not Resuscitate" tattooed over his left chest. What should the EP do?

The first step, as with the clinical situation, is for the EP to ask herself whether she has previously encountered—personally, through reading, or at conferences—this type of case. A number of these cases describing nonstandard advance directives, including tattoos, bracelets, and necklaces, have been described in the medical literature [15–17]. If she is aware of this, do they give her an ethically justifiable plan of action? For several reasons, nonstandard tattoos cannot be honored. The reasons include the unreliability of knowing whether the patient really wouldn't have wanted resuscitation in the current situation and whether the patient's situation since the tattoo was placed has changed. If she knows this and agrees, she should resuscitate.

If she does not believe that this case fits under any previously generated ethical rule, she should consider buying time for deliberation. Naloxone, artificial ventilation, and hydration would allow time to search for the patient's identity, medical records, and a possible surrogate if still needed. As described elsewhere in this chapter, initiating these interventions does not mean that they cannot be withdrawn if additional information makes that choice reasonable.

If the EP does not feel that this is reasonable, she can select what she considers the best ethically appropriate option and use the three tests to evaluate that choice. (Impartiality Test) If we assume that she chooses not to resuscitate, she should ask herself (Impartiality Test) whether she would want to have clinicians let her die (the patient is being kept alive with bagging) if she was the patient with an

uncertain diagnosis, history, and wishes. That is unlikely. If she says no, then she must go to another choice, such as to resuscitate. (Impartiality Test) Would she approve of that choice for herself? (Universalizability Test) Would she approve all other EPs resuscitating in similar situations? (Interpersonal Justifiability Test) Would she be willing to defend this action to her peers, superiors, or the public? If all three answers are in the affirmative, she should proceed with the assurance that she will be within the spectrum of ethically appropriate actions.

Bioethics Committees and Consultants

Another resource for complicated ethical dilemmas is to use your institution's bioethics committee. Most US hospitals now have multidisciplinary committees or bioethics consultants to help resolve bioethical dilemmas. Bioethics committees and consultants have four roles: (a) education, (b) policy development (proactive ethics), (c) retrospective case review, and (d) concurrent case review (ongoing clinical cases in which they often mediate between dissenting parties) [20]. Some experienced committees and consultants also perform "stat" consultations that can assist in emergency department cases.

Other Principles and Virtues

Other mid-level bioethics principles and virtues often guide clinician behavior. They also may conflict with the principle of autonomy or with each other, posing a bioethical dilemma. In their practice, emergency clinicians commonly use the principles of beneficence and nonmaleficence, as well as the virtue of truth telling. When developing policy, they often use the principle of distributive justice. Therefore, it is instructive to examine how these principles relate to specific clinical scenarios with ED patients, including those with hematologic or oncologic illnesses.

Beneficence is the principle of doing good or producing benefits. This principle is one of the medical profession's universal tenets. Society's view of physicians as altruistic reflects the profession's long history of beneficence. In addition, all medical students are taught the basic tenet of nonmaleficence: *primum non nocere* (first, do no harm). This stems from recognizing that physicians can harm, as well as help, their patients.

Clinicians use the principle of distributive justice to develop policies, including triage protocols, affecting patient groups and healthcare systems. Truth telling is the virtue that guides clinicians in what and how they communicate with patients and families, rather than the decisions they must make.

Beneficence

Clinicians enter the healthcare field to help others—to be beneficent or to do good. While ED interventions for hematology-oncologic patients will not provide a long-term solution, they often relieve symptoms or provide time to begin more definitive treatments. However, when opportunities to clearly benefit a patient present themselves, clinicians feel intense anguish when a patient or surrogate decision-maker refuses the interventions. This sets up a struggle between patient autonomy and physician beneficence. Probably the most common ethical dilemma in modern US medical practice, it exemplifies physician paternalism, that is, the desire to do what he or she thinks is best for the patient no matter what the patient (or surrogate decision-maker) wants.

Yet, when made by patients with decision-making capacity, clinicians should respect these refusals. That does not mean that the clinician should not clearly explain the options, potential outcomes, and costs involved. If the patient holds firm to the decision, the clinician must follow the patient's wishes, even if they conflict with his or her own values. This is the most difficult part of adhering to patient autonomy.

The only exceptions to this are when a surrogate makes a decision that the clinician believes is contrary to the patient's expressed wishes or is masking (possibly illegal) ulterior motives, or when a child is involved. In any of these situations, obtain legal assistance immediately. In the case of a child, including religion-based refusals of treatment, most courts will order clinicians to institute therapy if any reasonable chance of benefit exists.

Beneficence: Withholding and Withdrawing Treatment

As noted above, resuscitating patients who present to the ED with unknown illnesses and injuries is both ethically appropriate and virtuous behavior. A common fear, and unfortunate misunderstanding, is that once treatment is initiated, it cannot be withdrawn. Actually, there is a much higher ethical and legal bar to withholding treatment in uncertain cases than there is to withdrawing treatment once complete information is known [21, 22].

Withholding Treatment

Not infrequently, a patient is brought into the ED in extremis, unable to interact with clinicians, and without any history or direction about care. For example, the patient may be in cardiorespiratory failure or the patient may have metastatic cancer and now is suffering from hypercalcemia, a frequent terminal event. While some have advocated that allowing the patient with hypercalcemia to have a "good death" may be humane and medically appropriate [23], EPs

do not have this option. Without knowing the patient, the disease prognosis, or any prior wishes, they are obligated to intervene to preserve life. This obligation is based on the principles of beneficence and nonmaleficence, which are societal values placed on EPs. Our society sees the entire emergency medical care system as being the caregivers of last resort. Arbitrary decisions to do less than everything reasonable to preserve a life signal a lapse in this entrusted function. Unknown and unknowing patients deserve the presumption of life.

Withdrawing Treatment

Contrary to popular myth, if the EP (or inpatient physician) later learns that, given the patient's condition or wishes, lifesaving interventions such as ventilation and vasopressors are not appropriate, it is both ethical and legal to withdraw them. This follows the dicta to use only beneficial interventions and to preserve a patient's autonomous wishes. Morally, withdrawing treatment is identical to initially withholding it. That is, withdrawing an IV drip or stopping a ventilator is equivalent to withholding the next drop of medication or the next ventilation. The problems that generally arise with withdrawal under these circumstances are emotional, not ethical [21].

Even though treatment has been withdrawn, clinicians must continue to provide analgesia and any other appropriate care. Healthcare professionals never cease providing care.

Beneficence Versus Patient Autonomy: Refusing Lifesaving Treatment

As the relatively common case described in Case 1 demonstrates, the ethical dilemma is produced by the tension between the physician's motivation of beneficence and the patient's (or surrogate's) desire to determine which treatments to authorize based on his or her values. In this case, the decision is religiously based.

Beneficence Versus Patient Autonomy: Refusing Analgesia

Physicians are expected to follow the medical maxim "cure sometimes, relieve often, comfort always" [24]. In some cases, patients or their surrogates may refuse analgesics to relieve acute pain. This may be due to misguided concepts of drug abuse and addiction or to a fear that taking analgesics will hasten death. Rarely, refusal may stem from religious or cultural values.

The final decision may come down to a balance between autonomy and beneficence. While there may be unique instances when analgesics should be withheld, at least in the short term (e.g., so that the patient can be awake when relatives arrive), beneficence generally outweighs any countervailing argument and the patient should receive analgesia.

Nonmaleficence

The principle of nonmaleficence includes not doing intentional harm to patients, preventing harm, and removing harmful conditions. Nonmaleficence is the profession's protective shield for patients. The following two situations demonstrate how this may not only conflict with other principles, such as autonomy, but also how it forms the basis for the rules regarding clinical research.

Nonmaleficence: Demands to "Do Everything"

No one gets every possible medical intervention. Yet, ED clinicians commonly hear surrogates demand that they "do everything," even for terminally ill hematology-oncologic patients for whom further intervention will not change the disease course and may prolong an unpleasant dying process. This request, often coming from distraught and guilt-stricken relatives, poses difficult ethical dilemmas for clinicians. While patient autonomy plays a key role in any decision, surrogates may be unaware that clinicians' interventions must not harm the patient without providing them with a countervailing benefit (nonmaleficence).

The "do everything" request usually presents as one of three scenarios: where a patient knowingly requests intervention, where a patient asked for intervention via an advance directive, or where surrogates ask for the intervention.

The first situation occurs when a patient with decisional capacity who is informed of the options selects a probably non-beneficial and definitely painful course of therapy. In the ED, that may mean intubating and ventilating a terminal cancer patient in severe pain. These decisions fall under the question of patient autonomy, and even if the physician thinks she would not make the same decision herself, she should help the patient implement this choice.

The second scenario occurs when a patient has left instructions via an advance directive to "do everything." This directive carries much less weight than the patient's actual informed decision, described above, because the exact situation with which the medical team is presented could not have been anticipated. Nevertheless, clinicians should make all reasonable efforts to comply with the patient's wishes. The following case illustrates just such a dilemma for the EP.

Case Study 3

A patient with decision-making capacity completed a new Durable Power of Attorney (naming her husband as surrogate) and a Living Will upon entering the hospital three weeks earlier for the treatment of metastatic breast cancer. Both documents indicate that she wants everything possible done to save her life. She now comes to the ED with mark-

edly diminished consciousness, bradycardia, dehydration, but a normal respiratory rate. Her husband accompanies her. Suspecting hypercalcemia, the EP prepares to initiate normal saline hydration and appropriate laboratory studies when he receives a call from the patient's oncologist who tells him to do no studies or interventions. When informed about the advance directives and the potentially correctible condition, he says that he and another physician agree that nothing more should be done for this patient, despite what any documents or surrogates say.

Although some institutional policies now suggest that two physicians can initiate a Do Not Attempt Resuscitation order that countermands a patient or surrogate's wishes, this violates both ethical and legal norms. The EP's role is to provide potentially beneficial treatment (and care) whenever practicable. Admitting physicians may later wish to do otherwise, but that is between them, the family, the bioethics committee, and, ultimately, the legal system.

The third situation occurs when families of a terminally ill patient demand non-beneficial care for their relative. Emergency physicians are usually reluctant to provide this, since it only prolongs the predictable dying process. On the other hand, to be beneficent, clinicians frequently admit end-stage cancer patients if they come for pain relief that cannot be provided at home, to temporarily relieve a family of the stress of caring for the patient (respite care), as an interlude to get a patient into a hospice or nursing facility, or who are in the terminal stage of the disease presaging death. However, interventions which simply prolong dying usually violate the ethical principle of nonmaleficence.

Legally, the representative for a patient lacking decisional capacity can make any informed decision that the patient could make about healthcare. After explaining the options and that the interventions will not be beneficial, physicians should abide by these surrogates' requests, even if they seem unreasonable. Note, however, that a physician is never required to offer any treatment through a surrogate that they would not offer directly to a patient, such as cardiopulmonary resuscitation in an imminently dying metastatic cancer patient. This is a struggle between autonomy and nonmaleficence, and the medical team's responsibility is to follow the legal surrogate's instructions to the extent that they would follow a patient's instructions. The assumption is that in most cases, the patient believed that this individual would best represent his or her wishes. When clinicians question whether the agent is acting in the patient's best interest, they can ask a court intervene.

Nonmaleficence and Autonomy: Research Protocols

The horrors inflicted under the guise of scientific research during World War II led to the Nuremburg Code and subsequently the Helsinki Declaration, enumerating basic ethical principles for research studies [25]. Based on autonomy, the respect for persons as individuals, these research principles arose from the desire to no longer harm research subjects, as had been done both during WWII and subsequently in the civilian sector.

Research is vital to medicine. In the past, most medical care, including that in emergency medicine, has relied on experience that was unsupported by investigation, so-called nonvalidated practice. Recently, however, clinicians have begun to use evidence-based medicine, which requires research. Over the past three decades, research done within emergency medicine and that done elsewhere but applied to emergency medical practice has improved the elegance of patient encounters, significantly benefiting ED patients. In hematology-oncologic, research has driven diagnostic and treatment breakthroughs, and EPs can often assist in these projects.

Yet some aspects of clinical research and research oversight fall short of meeting the ethical standards of safety and patient benefit. Overall, emergency medicine research has been and continues to be a moral endeavor. Even more important than the institutional safeguards, such as the institutional review boards (IRBs), is the individual researcher's moral compass, which must serve to protect the subject-patients of clinical research. Perhaps the greatest moral lapse has been the lack of attention to key populations, such as women and children, within emergency medicine research, with the result that patients most needing acute intervention are the ones who suffer [26].

Funding availability, both from private industry and from government agencies, still drives research agendas. This raises questions about clinical researchers' fiduciary responsibility to their subject-patients.

Finally, the moral responsibility to ensure that any research protocol and its execution are ethical extends to the journals in which the research is published [27]. While emergency medicine has an excellent record of ethical research, a large percentage of human research studies published in the major EM journals fail to mention either IRB review or informed consent [26, 28].

System Constraints: Distributive Justice and Confidentiality

Distributive or comparative justice suggests that comparable individuals and groups should share similarly in the society's benefits and burdens. In contrast to the judicial system's retributive and compensatory justice, this basic bioethical principle does not apply to individual practitioners for ad hoc use in limiting healthcare resources for individual patients [29]. Rather, it is meant to be used at the policy-making level to allocate limited healthcare resources.

For example, triage decisions conform to this principle when they are applied uniformly and impartially to all

patients [30]. Other typical issues in emergency medicine for which distributive justice plays a part in designing policies and protocols include admission prioritization; how to work with patients who cannot pay for treatment; have the "wrong" insurance, or belong to the "wrong" medical system or group for the particular hospital or clinic; intentional or unintentional release of patient information; and how to work with patients who are undocumented aliens.

Other principles have also had long-standing importance to medical practice, one of the most important being confidentiality, that is, the nondisclosure of patient information. Based on a respect for persons (as is autonomy), patient confidentiality has been a cornerstone principle of the medical profession since antiquity. The *Hippocratic Oath*, for example, states, "Whatever, in the course of my practice, I may see or hear (even when not invited), whatever I may happen to obtain knowledge of, if it be not proper to repeat it, I will keep sacred and secret within my own breast." Confidentiality presumes that, unless they first obtain the patient's permission, physicians will not reveal to any other person or institution what patients tell them during the medical encounter. Various US federal and state laws have both emphasized (e.g., Health Insurance Portability and Accountability Act of 1996, HIPAA) and carved out exceptions (mandatory reporting) to this stricture. With the advent of minimally secure electronic medical records, the ability to maintain patient confidentiality has become even more difficult.

Note that privacy, often confused with but related to confidentiality, is a patient's right to sufficient physical and auditory isolation such that he or she cannot be seen or heard by others during interactions with medical personnel.

Truth Telling (Fidelity)

Truth telling remains a somewhat controversial virtue within the medical community. While many champion absolute honesty to the patient, honesty must be tempered with sensitivity and compassion; it should not equate to brutality. In recent years, poor role models, a lack of training in interpersonal interactions, and bad experiences may have diminished the perception of truth telling as a physician virtue. There are multiple tales of the champions of absolute fidelity who, nevertheless, were appalled by their own physician's lack of sensitivity when relating unfavorable medical news to them [31].

The degree to which physicians fail to disclose the truth varies with the circumstances. When failure to disclose the truth will do physical harm to the patient, such as in the infamous Tuskegee experiments on patients known to have syphilis, it is not only immoral but also probably illegal to withhold the information. Likewise, if failure to disclose information is strictly for the physician's benefit, such as telling a patient who calls in the middle of the night to "take two aspirins and call in the morning," although there is a strong suspicion of serious disease, there are serious ethical and legal deficits in the clinician's behavior. The issues become somewhat murkier when truth telling involves a third party, such as a sex partner who the patient has exposed to an infectious disease [32].

The following cases demonstrate two scenarios involving this principle that commonly occur with ED hematology-oncologic patients. The first deals with relating a probable diagnosis to a woman in a strong communitarian culture. The second deals with death notification, emphasizing the need for strong communication skills and sensitivity.

Truth Telling and Communitarianism: Diagnosis Notification

Case Study 4

A 54-year-old Hispanic woman comes to the ED with her family because of a persistent cough and poor health for at least the past several weeks. Before the patient can be examined or any tests performed, the patient's husband intercepts the EP and tells him that if the patient has a life-threatening disease, she is not to be told because "she doesn't want to know." The adult children agree. The evaluation shows that the woman has a hard new breast lump, honeycomb lesions, and multiple pulmonary nodules consistent with cancer. The physician has a policy to tell the truth to all his patients but believes that the family might be accurate in their assessment.

Many patients come from cultures that embrace communitarianism, rather than autonomy. Communitarianism stresses the interactions between group members, which may be just the family, but may also include elders, religious figures, or the entire tribe, group, or community. In this case, the family implied that the patient was part of such a culture.

Doing good in these cases often means respecting the patient's personal or cultural desire not to be explicitly informed about a serious disease. This is the norm for many Asians (particularly Japanese), Hispanics, and Native Americans. The enormity of this information (and slight possibility of error in this case), coupled with the minimal physician-patient relationship established in the ED, might also suggest that, at least at this stage, stating the presumed "diagnosis" could be avoided.

The question for the physician is, how much does the patient want to know? The best way to find out is to ask her both what she wants to know and, if she does not want to know anything, with whom does she want the physician to speak. If she wants the information, the physician is obligated to gently tell her what he knows about her illness,

including the next steps in the diagnostic process. If she designates someone else to receive this information, this fully complies with the patient autonomy principle and should be followed.

Truth Telling: Survivor Notification

Nowhere in emergency medicine is truth telling with sensitivity more important than when the clinician must deliver the news of a death, which is often an emotional blow, precipitating life crises, and forever altering the survivors' world. Emergency physicians must repeatedly do death notification as part of their daily work.

Case Study 5

A 63-year-old man who had been in remission with lung cancer presents to the ED in cardiac arrest. Bystanders had told the EMS personnel that he had been at the store when he suddenly became dyspneic and collapsed. They administered ACLS for 20 minutes without success. Without vital signs or cardiac activity, you pronounce him dead with a probable diagnosis of pulmonary embolus. You are notified that his wife and an adult child have arrived and were waiting in a side room. They do not know he is dead; it was unexpected.

Kind but direct notification has been shown to be what most US and Canadian families desire. Other cultures prefer more indirect notifications. Come in, sit (or kneel) so that you are at eye level with the key recipient—in this case, the wife. Be sure that you or someone on your team has definitively identified the people as the decedent's family. Then say, "I'm sorry, but I have very bad news. Despite doing everything we (includes paramedics) could, your husband died." Truth telling and survivor understanding require that you use a "D" word, no matter how difficult that is. Otherwise, the message you relay may not be clearly understood. "Pass on," "No longer with us," "Gone to another place," and other euphemisms will not work. Take a deep breath and say "died" [33].

The wife then asks two things: "What did he die from?" and "Can you call his brother in another state and tell him?" The first answer is generally straightforward. No matter what your clinical suspicion is, truthfully tell her that you cannot be sure and that finding out will require an autopsy. (In some situations, a medicolegal autopsy might be automatic. If not, you can encourage the family to ask for one.) Telling the brother also requires truth telling. Gently inform a survivor who is distant from the ED about the death. Don't say that he or she is "critically ill." That way they won't make a heroic, sometimes dangerous, attempt to get to the hospital "in time" [34].

Excellent communication skills represent the basis for correctly delivering tragic news to survivors. Directness, truth, consistency, and clarity are the key factors in delivering information about a sudden, unexpected death—and complying with the virtue of fidelity. Perceptive survivors can easily tell which notifiers care and which are only "going through the motions" [33, 34].

Poor clinician-patient communication disappoints both the patients and clinicians. Often, this failure is due to clinicians:

- Using highly technical language
- Not showing appropriate concern for problems voiced by patients
- Not pausing sufficiently to listen
- Not verifying that the listener has gotten the information presented
- Using a generally impersonal approach to the interaction, including their manner of speech [35]

Delivering the news about sudden unexpected death provokes strong emotions in both the notifier and survivors. Communication is improved if the notifier acknowledges those emotions, being prepared to vocalize and demonstrate their sadness and to recognize and acknowledge it in the survivors. Using the voice to communicate does not always mean talking. In some instances, para-verbal behavior is what is called for. These sounds, such as mmmmm, ahhhh, or mhmmm, are often sufficient to show that a person is listening and understands, particularly if they are accompanied by appropriate nonverbal cues, such as nodding the head.

It often takes imagination to put oneself in the position of a grieving survivor, especially when wide cultural or age differences exist. Even if you cannot learn to empathize with survivors, you can learn to behave appropriately, speak correctly, and assist them in their time of grief. Imagination, studying people, advance planning, or taking the lead from experienced mentors is the only way to successfully perform this necessary, but tragic task [33, 34].

Future Bioethics in EM and the Role for Emergency Physicians

No patient can receive every possible diagnostic or therapeutic intervention. The clinician's traditional role has been to determine which resources would most likely benefit particular patients. As these resources become more costly and, in some cases less available, insurers, healthcare institutions, and families have become part of this decision-making process. In the future, bioethics discussions will become increasingly vital to protect patients and the integrity of the healthcare system.

The bioethics field includes teachers, writers, and clinicians. Many individuals in the field are involved in more than one of these areas. People enter the field with a variety of backgrounds, the most common being medicine (e.g., physicians, nurses, and physician assistants), legal, religious, and philosophy. Many, if not most, individuals have additional training before embarking on a leadership role within bioethics. This may include fellowships, serving on an institutional bioethics committee, or working with an experienced mentor.

Those in clinical ethics need a grounding in the "Mid-Level Principles," as described in this chapter and elsewhere. In addition, especially for a leadership role, they should have a knowledge of group dynamics, negotiation, compassionate listening, and writing. All come into play in working with patients, families, other surrogates, treating clinicians, and healthcare institutions. Very few clinicians are reimbursed for their time doing clinical ethics.

Emergency physicians, partially due to their training and type of practice, have unique qualifications for clinical bioethics. Aside from their ability to negotiate (e.g., for admissions, consultations, special testing), they work with and are usually sensitive to the differences among multiple socioeconomic and cultural groups. Similarly, they work with and are generally familiar with a wide variety of healthcare professionals, institutions, and systems. All these elements often arise in the course of bioethical consultations, policy making, and clinical education.

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Health Disparities

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Marcia A. Perry and Joel Moll

Introduction

The impacts of inequities and social determinants of health that lead to healthcare disparities and leave many patients vulnerable to poor outcomes have been well documented in patient care. Factors such as access to care, societal bias and stigmatization, lack of autonomy, and social determinants of health, among others, contribute negatively to the effectiveness of the care provided.

The National Academy of Medicine 2002 report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* concluded that minority patients generally receive lower quality healthcare than white patients in the United States, regardless of insurance status or ability to pay [1]. The report noted that these disparities in quality of care were associated with more deaths among racial minorities than whites. These findings are part of the impetus to examine how structures, processes, and behaviors in our healthcare system may be contributing to disparities among multiple vulnerable groups.

Concepts and Definitions

Healthy People 2020 defines Health Equity as: "The attainment of the highest level of health for all people. Achieving this requires valuing everyone equally with focused and ongoing societal efforts to address avoidable inequities, historical and contemporary injustice, and the elimination of health and healthcare disparities" [2]. Health inequities are differences in health that are not only unnecessary and avoidable but are considered unfair and unjust. Health inequities are rooted in social injustices that make some population groups more vulnerable to poor health than other groups. As a result of health inequities, disparities arise in the presence of disease, health outcomes, or access to healthcare and therapies between population groups. Healthcare disparities are related to provider-patient relationships, provider and systemic bias, social determinants of health, and patient variables such as mistrust of the healthcare system due to past experience. The Minority Stress Model explains that minority groups experience chronic high levels of stress from stigmatization that can contribute to poor outcomes and disparities [3, 4].

Provider and systemic bias can either be explicit or implicit. Explicit bias is often easier to recognize as the outward expression of prejudice. Implicit bias, the unconscious attribution of qualities or values to a member of a certain group, can be much more difficult to recognize. These biases are shaped by experiences and based on learned associations between particular qualities and social categories. Many physicians have different exposures and backgrounds than the patients they serve. Unconscious attitudes and stereotypes affect behaviors and decisions in healthcare. In order to have greater awareness of bias in patient care, it is critical for physicians to receive education, feedback, and coaching on equitable practice.

The population of the United States is becoming increasingly more diverse, with racial and ethnic minority populations predicted to surpass the white majority by 2050. It is critically important that healthcare professionals are educated specifically to address issues of culture in an effective manner that will lead to equitable patient care. Emergency department (ED) patients are from multiple different identities and cultures. Achieving cultural competence in each culture and sub-culture is challenging and not feasible. Cultural *humility* is a more feasible and achievable goal for clinicians [5, 6]. Cultural humility is a lifelong process of self-reflection and self-critique that can inform understanding of cultural differences and how differences require sensitive approaches to healthcare. It requires that clinicians acknowledge how history, culture, and community intersect in the patient's

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experience. By understanding the power of storytelling and the power of intent, and by active listening and asking deeper questions, we gain a true understanding of the depth of the determinants of health so that we can provide the equitable care patients need and deserve.

Disparities and Cancer Care for Vulnerable Populations

Many vulnerable populations access the healthcare system through the ED, providing both an opportunity and obligation to providers in this setting to deliver equitable care. Patients who present to the ED and are diagnosed with cancer tend to have more advanced conditions, leading to worse outcomes [7, 8]. In one study, patients initially diagnosed with cancer in the ED were 75% more likely to present at stage 4, and 176% more likely to die within 2 years of presentation than those receiving a cancer diagnosis in other settings [7]. ED-diagnosed patients were more often black or from impoverished urban areas [7].

The American Society of Clinical Oncologic has published policy statements outlining the following strategies to eliminate cancer health disparities [9].

- Access to quality healthcare – address economic barriers for minorities and the underinsured as well as healthcare delivery.
- Improve healthcare provider, public, and policy maker awareness of racial and ethnic disparities in access to cancer care and outcomes.
- Diversify the oncologic workforce.
- Conduct research to understand the differences in quality of cancer care provided to underserved and ethnically diverse population compared to whites.
- Diversify clinical trials.
- Enhance patient involvement in their care.

Application of these strategies to emergency medicine can help reduce these inequities. As advocates for our patients, we should work consciously to decrease bias, be intentional in diversifying our work force, engage patients in clinical trials, conduct healthcare disparity research, and use cultural humility to provide patient-centered equitable care.

The following cases illustrate concepts of healthcare disparities in vulnerable populations.

Case Study 1

A 56-year-old transgender female arrives to the ED with non-traumatic mid lower back pain. There is no associated weakness, parethesias, or bowel or bladder dysfunction. There is no fever, no past history of intravenous drug use (IVDU). Patient denies medications except estrogen and spironolactone as gender-affirming therapy. Patient was seen and discharged with ibuprofen.

She returns 2 weeks later as the back pain has worsened, and she has now noted some blood in her urine. A clean catch UA shows >100 RBCs and 5 WBCs. She denies dysuria but has some hesitancy. She is placed on nitrofurantoin and discharged.

She returns a week later very uncomfortable and unable to urinate with bilateral flank pain. Bladder scan reveals a markedly distended bladder. She is much improved after decompression with a catheter. A renal CT scan shows multiple lytic lesions in the lumbar spine and a markedly enlarged and irregular prostate, findings consistent with metastatic prostate cancer.

Sexual minorities are a diverse group of individuals without a strict heterosexual identity (lesbian, gay, bisexual, queer or questioning) and/or whose gender identity is different or fluid from their sex-based gender. It is important to recognize that someone's sexual or gender identity may be different from their expression or their behavior. One estimate is that 4.5% of Americans identify as a sexual minority [10] and at least 0.6% as transgender [11]. However, 8.7% of women and 8.2% of men have had same-sex sexual behavior [12].

Sexual minorities have specific health needs intrinsic to their sexual orientation, gender identity, and behavior, in addition to healthcare requirements of the general population. Sexual minority patients face several barriers that may contribute to healthcare disparities, affect their visibility, and impact their relationship with physicians. Historical mistreatment and discrimination, combined with current implicit and explicit bias, can adversely impact the ED experience or decision to seek care at all. Several studies have reported that sexual minorities commonly have negative experiences in the ED, especially in the transgender community [13, 14]. Healthcare benefits and rights may not be extended to sexual minorities. There is not protection against job discrimination in many states, nor at the federal level. Many sexual minorities fear that disclosure of their identity may affect their employment and also their healthcare coverage. Sexual minorities consistently have less access to healthcare, are less likely to be insured, and are more likely to live in poverty.

Transgender patients may have additional identity barriers. They may be listed as their gender assigned at birth in the health record, rather than their gender identity. Many transgender patients do not have identity documents with their preferred identity, with the biggest barrier being cost [15]. This can lead to awkward interactions when the patient appears different than the gender listed in electronic health records (EHR). Importantly for the patient in the case above, the EHR and provider may not have triggered reminders for prostate screening if the patient was listed as female. The patient may not have had gender-affirming surgery to remove

her penis, and even if so, most surgeries do not remove the prostate.

Most emergency physicians receive little if any training on sexual minority health in residency [16] and have limited knowledge from medical school [17]. Emergency medicine residents often do not ask about sexual behavior or identity when pertinent, such as the evaluation of an abdominal or GU complaint [18]. Practicing emergency medicine physicians demonstrate poor knowledge of transgender health [19]. Although limited, research suggests that knowledge gaps contribute to important unmet needs in sexual minority patients with cancer [20, 21].

Competent care of sexual minority patient involves not only knowledge, but importantly communication and attitude. When approaching a sexual minority patient with a known or possible diagnosis of cancer, communication and inclusion are important initial considerations. Using language and terminology that is open and not inadvertently offensive is paramount to establishing a trusting and effective relationship. An inclusive environment should be established by using neutral terminology rather than assuming heterosexual and gender concordant identity. Patients should be permitted to include their spouse or significant other if desired, as with any heterosexual couple. When in doubt, ask the patient to define relationships and preferred name.

When taking a history, it is important to focus on information needed for competent care of the patient and avoid irrelevant questions. In the above case, it is clearly relevant to inquire whether the patient has had gender-affirming surgery as it may relate to their presentation or management of genitourinary complaints. In addition, placement of a catheter may be more complex if the penis has been removed and the area has been reconstructed. But for the same patient with an ankle sprain, asking about gender-confirming surgery is more likely curiosity than medical necessity. Similarly, performing a physician exam that is unnecessary due to inappropriate focus is not only unethical but a violation of the patient's trust and would be a damaging experience.

Sexual minorities have been largely overlooked in research on cancer disparities. Disparities have been found with cancers associated with viral infections in men who have sex with men (MSM) [22], including elevated risk for anal cancer, especially in HIV-positive MSM [23]. Although it is postulated that lesbians may have higher rates of breast and reproductive cancer due to possible increased nulliparity, lack of routine collection of sexual orientation data has made determination problematic [24]. Gender-affirming hormone therapy has not been definitely linked to increased breast and reproductive cancer risk in a small number of studies [25]; however, there is some suggestion that when it occurs, breast cancer in transgender females may occur at a younger age (median 51.5 years) [26]. Sexual minorities have higher rates of tobacco abuse, and limited data shows this may translate into higher rates of lung cancer [27, 28].

Evaluation and management of a sexual minority with known or possible cancer diagnosis in the ED can add additional complexities and requires basic competency in treatment of this patient population. Competency in sexual minority healthcare requires the acquisition of knowledge and skills, as well a positive therapeutic attitude, to provide equitable and optimal care.

Key Points

- Sexual minority patients are a diverse group along a continuum of sexual orientation not strictly heterosexual and/or gender identity different than gender assigned at birth.
- Sexual minorities face many healthcare and legal barriers than can adversely affect access to care and may adversely affect outcomes.
- Emergency physicians receive little training on healthcare of sexual minorities. Basic understanding of healthcare needs, barriers, terminology, and inclusive communication are important to deliver more equitable care.

Case Study 2

A 48-year-old black male with no significant past medical history presented to an urgent care center for rectal bleeding. He is self-employed and has no health insurance. He plows snow in the winters and does lawn care in the summers.

He had stable vitals, has a normal hemoglobin, and was diagnosed as having hemorrhoids after a small external hemorrhoid tag was noted on exam. He was prescribed a cream to shrink the hemorrhoid and was discharged. He has intermittent small amounts of blood in his stool over the next 2 years.

Two years later he presented his local ED stating that his "hemorrhoid was acting up," and he was prescribed a rectal suppository for internal hemorrhoids after a small hemorrhoid tag was again noted. He was told to follow up in the gastrointestinal (GI) clinic if bleeding returns. He called the GI clinic a month later to schedule an appointment and was told they would not see him without insurance and told him to go to the county hospital clinic. The county hospital clinic had no appointment for 6 months. During that 6-month period, he lost his mother, and his adult daughter moved back home, so he missed his appointment due to multiple competing home issues.

One year later, a family member visiting from out of town noted that he had lost weight and was jaundiced, and convinced him to go to the urgent care center. He was sent from the urgent care center to the ED for work-up of anemia and jaundice. After 6 hours in the ED, he was diagnosed with metastatic cancer, which was later confirmed as metastatic colon cancer. He underwent two rounds of chemotherapy before his death.

Colorectal cancer is the third leading cause of cancer deaths in the United States for both men and women. It is largely preventable by timely screening of at-risk groups. The gold standard screening tool, screening colonoscopy, was previously recommended by the American College of Physicians for individuals 50 and over. Due to a recent increase in young individuals under age 50 with colorectal cancer, and a significantly higher risk of colorectal cancer in blacks, it was further recommended that blacks be screened starting at age 45 years. Recently, the American Cancer Society changed screening recommendations to start at age 45 in all individuals irrespective of race and ethnicity. The patient above was not initially referred for colorectal cancer screening and subsequently encountered significant barriers to diagnosis. Minority groups have a lower rate of endoscopic screening recommendations [29]. Socioeconomic status and access to healthcare help account for racial and ethnic disparities in colorectal cancer screening [29]. Patients are more likely to be referred for endoscopy if over age 55, white, with a family history of colon cancer, married, more education, an income greater than $65K, more frequent doctor visits, and female. Hispanic patients were 34%, and blacks 26% less likely than whites to receive a referral for screening colonoscopy. In summary our patient finds himself in the at-risk group for disparate referral for several reasons: he is under 50, is black, has a low education level, is in the low-income category, has no insurance, and is male.

Along with the new recommendations for a lower threshold for screening to age 45, improved education of emergency physicians on risk factors for colorectal cancer in vulnerable populations as described above is needed to lessen cancer healthcare disparities. This patient had several missed opportunities to receive referrals for screening and avoid what may have been a preventable death.

Key Points

- Colorectal cancer screening should begin at age 45.
- Referral for colorectal cancer screening should be done from the ED for at-risk patients.
- At-risk patients can be identified through social determinants of health questions.

Case Study 3

A 26-year-old female with a history of schizophrenia presents to the ED. She was previously seen in the ED at age 18 after sexual assault and was examined and treated. Eight months later she presented with a complaint of pregnancy and not feeling the baby moving. She had a flat abdomen and a negative pregnancy test and was discharged with a diagnosis of paranoid delusions and referred to psychiatric resources. Over the next few years, she was seen and admitted several more times for delusional psychosis. She was then managed well in the outpatient psychiatric clinic; however, she began presenting again to the ED with abdominal pain and swelling at the age of 24. She had multiple negative pregnancy tests and referrals to psychiatry. Finally she presented to the ED with a court-appointed guardian who insisted on a more thorough medical evaluation because the guardian was convinced that the patient was indeed pregnant. An ED physician who had seen her in the past felt that she had a protuberant abdomen and performed an abdominal ultrasound. Ultrasound revealed a large ovarian mass and the patient was subsequently diagnosed with ovarian cancer.

Patients with mental illness are at increased risk for cancer care disparities. Cancer incidence is similar in individuals with or without schizophrenia. Patients with schizophrenia are 1.5–2 times more likely to die of their cancer than patients without mental illness [30]. Patients with schizophrenia are also more likely to present at advanced stages of disease, are offered surgery at lower rates, and receive fewer chemotherapy sessions [30]. Patients with schizophrenia and other disabilities are often unable to advocate for themselves and are also at increased risk of experiencing physician bias. The 2016 Medscape Lifestyle Report surveyed 15,800 physicians across 25 specialties and found that 40% of physician admitted to bias toward specific types of patients. A higher proportion of emergency physicians reported bias (62%), and that their bias influenced patient care (14%) than any other specialty [31].

Educating emergency physicians regarding unconscious bias with ongoing discussion of methods to mitigate bias is one way to address and decrease the risk of disparate treatment in vulnerable populations.

Key Points

- Patient with schizophrenia are more likely to die of their cancer than patients without mental illness.
- Physician bias exists and emergency physicians admittedly have a high level of bias against patients with mental illness.
- Raising awareness of physician bias and how bias affects clinical decision making is key to helping physicians mitigate bias

Case Study 4

A 24-year-old black female first-year medical student presented to the ED with left chest and breast pain during her first month of medical school. No breast exam was done. Her ED evaluation included a normal chest radiograph and ECG, and she was told to follow up with student health services. At her follow-up she was told it was likely anxiety as

experienced often by early medical students. While at home for a holiday break, she saw her primary care physician for persistent left breast pain and a lump was palpated on exam. A biopsy was arranged and she received the unfortunate diagnosis of triple-negative breast cancer. She subsequently underwent left breast mastectomy followed by chemotherapy and radiation therapy.

Breast cancer is more prevalent among white women than black women. However, black women have a higher risk of breast cancer before the age of 40, higher risk of more aggressive cancer, and higher risk of poor outcomes. This largely unexplained disparity in breast cancer outcomes is an area of ongoing research [32]. Williams et al. explored the contribution of social factors (including minority stress) to breast cancer disparities in black women. They conceptualized that increased exposure to psychological stress, low socioeconomic status, and early life adverse exposures that black women experience may be the cause of current disparities in breast cancer incidence and mortality. Increased exposure to psychological stress resulting in epigenetic changes may increase breast cancer risk over one's lifetime. Discrimination and racism as a distinct social exposure experience by racial minorities is an area requiring additional research to separate the factors driven by racism and bias from those driven by socioeconomic status [32].

Key Points

- Black women have a higher incidence of breast cancer than whites before age 40, as well as a higher mortality risk.
- Discrimination, bias, and racism (and other minority stressors) are likely significant contributors to disparity in breast cancer and should be further studied.

Summary

Emergency physicians are trained to work in a high stress, fast-paced environment where the focus is on not missing life-threatening conditions. It is challenging yet necessary for us to find time to address social determinants of health and other barriers to good health and good outcomes. As the safety net for vulnerable population, emergency physicians must develop the skills to identity those at risk for healthcare disparities, consider and address their needs, and strive to eliminate healthcare disparities. Education, research, and advocacy are important priorities for health equity.

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Emergency Oncology in the United Kingdom

66

Tim Cooksley

Introduction

In the United Kingdom (UK), over 350,000 new cases of cancer are diagnosed a year, contributing to around 28% of UK deaths [1]. In the UK, patients with cancer account for 15% of all acute inpatient stays and its delivery consumes nearly half of the spending on patients with cancer [2].

Cancer care has become increasingly specialised, and advances in therapy have resulted in a larger number of patients receiving care as an outpatient. As a result of these advances in care and the increasing number of patients receiving cancer therapies, there has been a significant increase in the number of patients presenting with unscheduled cancer-related emergencies [3].

The management of emergency oncologic patients presents many challenges. There are toxicities of targeted and immune therapies with which acute care physicians may not be familiar. Early recognition of acutely unwell cancer patients at risk of clinical deterioration is important not only to instigate treatment but also to facilitate decisions regarding whether escalation of care and cardiopulmonary resuscitation is appropriate [4]. This requires an understanding of the patient's underlying prognosis and goals of care, which often requires oncological advice.

In the UK, there have been two strategies adopted to improve the care of acutely unwell cancer patients – the development of specialist admission units in tertiary cancer units and the evolution of "acute oncologic services" to support patients admitted to non-cancer hospitals.

Acute Oncologic Services

In 2009, following a series of reports recognising that a significant proportion of cancer patients presenting to UK Emergency Departments (ED) received sub-optimal care, the UK National Chemotherapy Advisory Group (NCAG) recommended that every UK hospital with an ED established an acute oncologic service [5]. As a result of the varying demands and resources available across the UK to develop acute oncologic services at each hospital, there has been a wide range of models employed to deliver this strategy. The core of all acute oncologic teams has been an acute oncologic specialist nurse coordinating the service often supported by visiting oncologists.

The fundamental principles of an acute oncologic service are to promote education, awareness and early access to specialist oncologic input. It aims to drive integrated working between acute care physicians, surgeons, medical specialists and oncologists. Acute oncologic supports the variety of ED presentations from initial diagnosis, treatment complications and end-of-life issues. These encompass the three clearly defined types of acute oncologic presentation:

- Type 1 – Patients who present with a new diagnosis of cancer
- Type 2 – Patients who present with toxicities related to cancer treatments
- Type 3 – Patients who present symptoms and complications related to the cancer itself

Despite many national initiatives targeting early diagnosis of cancer in the UK, around a quarter of new cancers continue to be diagnosed during an emergency admission [6]. These patients traditionally were at risk of poorly coordinated care with late referrals to oncologic and palliative care services. Acute oncologic services have played a fundamental role in supporting the management of these patients and ensuring diagnostic pathways are completed in a timely fashion. This is especially pertinent in patients presenting

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with malignancy of unknown origin who often experienced fractured diagnostic journeys with lack of continuity and clinical accountability [7].

A yearly review of a regional network acute oncologic service covering seven hospitals in the North West of England reported 3013 new patient admissions, of which 19% were type 1 admissions, 30% type 2 and 51% type 3 [8]. Acute oncologic models reduced the length of inpatient hospital stays and delivered significant cost savings [8, 9].

Specialist Cancer Admission Units

Case Study

The Christie National Health Service (NHS) Trust is a tertiary oncologic hospital and is one of the largest in Europe. It has 250 beds including a 21-bed Oncologic Assessment Unit (OAU) and a 7-bed Critical Care Unit. It is the lead cancer centre for patients in Greater Manchester and Cheshire but provides many national services.

The OAU is a hybrid urgent care centre/observation unit based on the UK Acute Medical Unit (AMU) model of care, and 30–35% of patients are discharged directly with the rest admitted to downstream inpatient wards [10]. *The OAU does not admit patients with symptoms suggesting an acute cardiac event or those who may require emergency surgery. These patients are diverted to their local ED.*

A general AMU acts as a 24/7 hub for all emergency medical admissions to hospital and provides a gateway to medical specialties, including oncologic. Its core processes are similar to those in an ED including initial assessment by a competent clinician, early review by a senior clinician, diagnosis with early access to diagnostic tests, assessing and stabilising physiological instability (for a period of up to 48 hours), care delivered by a specialist multi-disciplinary team and triage to appropriate downstream wards if the patient requires an anticipated inpatient stay of greater than 48 hours.

The OAU currently admits around 450–550 patients a month. Patients are admitted to the unit through three main routes:

1. **Via *a hotline/paramedics*** *– All patients receiving treatment at The Christie have access to a specialist helpline, run by nurse specialists. Patients are advised that if they develop symptoms, such as fever post-chemotherapy, they contact the hotline for advice and assessment. If they are triaged as having a condition related to the cancer or its treatment, they are admitted to the admission unit for assessment. This is often facilitated by the hotline contacting an ambulance to transfer the patient to the hospital.*
2. **Via *inpatient clinics/chemotherapy/radiotherapy.***
3. **Via *referrals from other hospitals*** *– Patients under the care of The Christie or with an acute cancer presentation at another hospital who need urgent chemotherapy/specialist inpatient care are referred to The Christie and transferred to the admission unit.*

The OAU is staffed and supported by acute care physicians and advanced nurse clinicians with expertise in emergency oncologic presentations, medical and clinical oncologists, haematologists, supportive and palliative care physicians, visiting medical specialists with interests in complications of cancer therapy, experienced acute oncologic nurses and allied health-care professionals. This model facilitates timely and high-quality tertiary acute oncologic care with a focus on personalised emergency cancer care. It also facilitates innovations that are essential to the delivery of emergency oncologic care, such as triage nurse-led delivery of first-dose intravenous antibiotics in patients presenting with sepsis [11]. *One of the strengths of our centre is significant acute care physician and specialist experience in managing acutely unwell patients with immune-mediated toxicity alongside oncologic colleagues, as well as managing the multitude of medical presentations. This ensures high-quality outcomes for acutely unwell cancer patients.*

Ambulatory Care

Ambulatory care is recognised as a key tenet in ensuring the safety and sustainability of acute care services. The fundamental basis for ambulatory care is that patients presenting with acute illnesses can be stratified as low risk for developing complications and therefore do not require traditional inpatient care [12]. The NHS targets that 25% of all acute medical presentations are managed through this route.

There are an increasing number of acute cancer presentations that can be risk assessed for care in an emergency ambulatory setting. These include low-risk febrile neutropenia, incidental pulmonary embolism, cancer-associated DVT, chemotherapy-related acute kidney injury, chemotherapy-induced nausea and vomiting, indwelling line infections, acute management of pain crises, malignant hypercalcaemia and other electrolyte abnormalities, asymptomatic brain metastases and malignant pleural effusion [13–15].

Ambulatory models offer the opportunity to integrate palliative and supportive care with oncologic and acute services. Ambulatory enhanced supportive care models have shown utility in the management of low-risk febrile neutropenia [16]. This appears to facilitate improved access for patients to expertise in cancer care and immediate management of the complications of cancer treatment with the goal

of preventing downstream complications and future emergency presentations.

Modelling of ambulatory emergency oncologic services with integrated expert supportive and palliative care services is key for providing high-quality, personalised and sustainable emergency oncologic care. It enables a greater number of patients to have their cancer complications managed at their cancer treating centre and aims to reduce attendances at overcrowded general EDs.

UK Role in International Emergency Oncologic Research

The optimal medical management of many cancer-related emergencies is a key area for further research. Many practice patterns are based on expert opinion or prior experience rather than clinical trials. These include traditional presentations such as the management of opioid-related constipation and rescue therapy for chemotherapy-induced nausea and vomiting.

Prospective trials into the emergency management of immune-mediated toxicities of immune checkpoint inhibitors examining optimal doses of steroids for those presenting with life-threatening toxicities and the timing of steroid-sparing agents, such as infliximab, are essential. It is key that these studies are not only multi-national but supported by acute care physicians working in emergency oncologic settings.

The care model used for patients with oncologic emergencies needs to be tailored to the local medical and oncologic environment; therefore, it naturally follows that different medical systems have developed different processes to care for these patients. A key for successful emergency oncologic models is the underlying goal of care being provided to these patients by clinicians who are knowledgeable about their needs and have integrated communication with the primary oncologists. Acute care of the oncologic patient is gaining recognition as an important international area that could be improved upon with increased training, research and emphasis on integration into the oncologic system. International collaboration is needed to achieve this.

COVID19 and Acute Cancer in the UK

At the time of writing, the impact of COVID19 on emergency oncologic is unclear. The COVID19 pandemic has resulted in the redeployment of many acute oncologic staff into non-oncologic-based roles to help with its management. The impact and duration of these changes is not yet understood.

Furthermore, the outcomes relating to acutely unwell cancer patients with COVID19 and their optimal management is a new challenge for those working in emergency oncologic. Modelling so that patients with SARS-CoV-2 are not co-located with those without will have significant implications for the delivery and modelling of acute cancer services in the UK and internationally. The specialist cancer ER in Asan, Seoul, South Korea, has already been reconfigured to become an infectious diseases/COVID19 ER for the foreseeable future.

It is too early to speculate as to the long-term impact on emergency oncologic services of COVID19, but no current chapter relating to this subject would be complete without a brief caveat suggesting that significant changes in modelling may be necessary.

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Cancer Pain Management in Low-Resource Settings

67

Shiraz Yazdani and Salahadin Abdi

Case Study

A 68-year-old female in a low-resource setting presents to a general practitioner clinic with severe back pain. Upon performing a history and physical examination, the provider finds a large mass on her left breast that is highly suspicious for a malignant process. The patient states that she has had the mass for several years but did not seek care due to fear of being shunned by her community for having this abnormality. Further diagnostic testing reveals an invasive ductal carcinoma which has metastasized to the liver and bony structures including vertebral bodies, causing an acute vertebral compression fracture, which explains the patient's severe back pain. The patient begins treatment for her malignancy with a local oncologist but continues to have severe back pain despite conservative measures. Due to lack of available trained personnel, she is unable to undergo vertebral augmentation to treat her compression fracture. Her team attempts to control her pain with a combination of opioids and adjuvant medications. However, due to regional restrictions on opioid importation, her treatment options are limited to tramadol, codeine, and immediate-release morphine sulfate. Healthcare providers attempt to get approval for transdermal fentanyl in order to improve her pain control but are unable due to the cost to the hospital and clinic system for importing this medication. They also find a provider who can perform vertebral augmentation to improve her pain, but that facility is several hours away and the patient states that she cannot afford to travel there. Furthermore, there is a lack of governmental assistance programs to help patients such as her travel to seek more advanced care.

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Introduction

Despite advances in the treatment of cancer, a large proportion of oncologic patients report disease-related pain at some point during the evolution of their disease process. The incidence of cancer-related pain increases with more advanced disease. Suffering from this pain can significantly impact a patient's activities of daily living and quality of life [1]. Despite advances in the treatment of various cancer disease processes, as well as the numerous etiologies of cancer pain, uncontrolled pain remains a significant issue. The prevalence of pain has been reported as 64% in those patients with advanced disease. Even in cancer survivors, the prevalence has been as high as 33% [2]. Treatment of cancer and cancer-related pain varies based on geographic differences in availability of information, training of healthcare workers, and availability of resources (equipment for interventional procedures, medications for pharmacologic treatment, appropriately trained providers for non-pharmacologic management, etc.). In certain settings, resources can be limited. This can lead to significant alterations in the availability and applicability of treatments for cancer pain. The vast differences in resources can be attributed to unequal distribution of power, income, goods, and/or services [3]. These differences occur within and between countries. Certain populations have been reported to be at higher risk for such inequalities including those with low-income, minorities, and underserved women [4]. On a global scale, many low- and middle-income countries experience this low-resource environment, and patients in those countries may suffer from untreated or undertreated cancer pain. The primary countries associated with the most readily available resources include Western Europe, North America, and Oceania [5]. Roughly, countries can be classified according to their human development index as compared to other countries. This composite includes components of life expectancy, education, and per capita income [6]. Although diagnosis and treatment in these settings may be challenging, it is critical to strive to provide the same level of care across the board. In an effort to highlight this goal, the

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United Nations has released Sustainable Development Goals for 2030. These goals call for a reduction in premature mortality by a third using appropriate prevention and treatment modalities [7]. In this chapter, we highlight cancer pain and its treatment, ranging from etiologies and modalities of treatment to challenges and opportunities in low-resource settings.

Etiologies of Cancer Pain

Understanding and treating the etiologies of cancer pain requires a detailed understanding of the assessment of the cancer pain patient [8]. This is particularly important in the low-resource setting, as patients in these settings can present unique challenges in terms of education levels, expectations, social situations, family dynamics, and cultural belief systems. Beginning at the most basic level of assessment lies the chronicity of pain. Even at this level, patients in low-resource settings may present in a later stage of chronicity due to low access to care [9]. This lower level of access leads to many patients in low-resource settings to be diagnosed at later stages of disease [10], which is associated with higher levels of pain. Additionally, cancer pain is a unique type of pain that often evolves at a rapid pace. It requires consistent re-evaluation and re-assessment. These constant changes may be from a change in the disease process (e.g., tumor growth or metastasis), response to treatment (e.g., reduction of tumor burden), treatment of pain generators (e.g., nerve blocks), adverse reactions to treatment (e.g., chemotherapy-induced peripheral neuropathy), side effects from medications (e.g., myalgias), or a combination of any of these issues. This constant re-assessment requires significant resources but is critical in treatment as the etiology of pain can shift quickly in a patient with cancer (Fig. 67.1).

The most basic place to begin with the etiologies of cancer pain is determining the pain's cause and pathophysiology. Syndromes are often used to describe commonly associated states in cancer pain [11], but a universal classification system for these syndromes has not yet been determined [12]. A simple way to classify different types of pain is whether they are related to tissue damage (somatic nociceptive, visceral nociceptive) or nervous system disorders

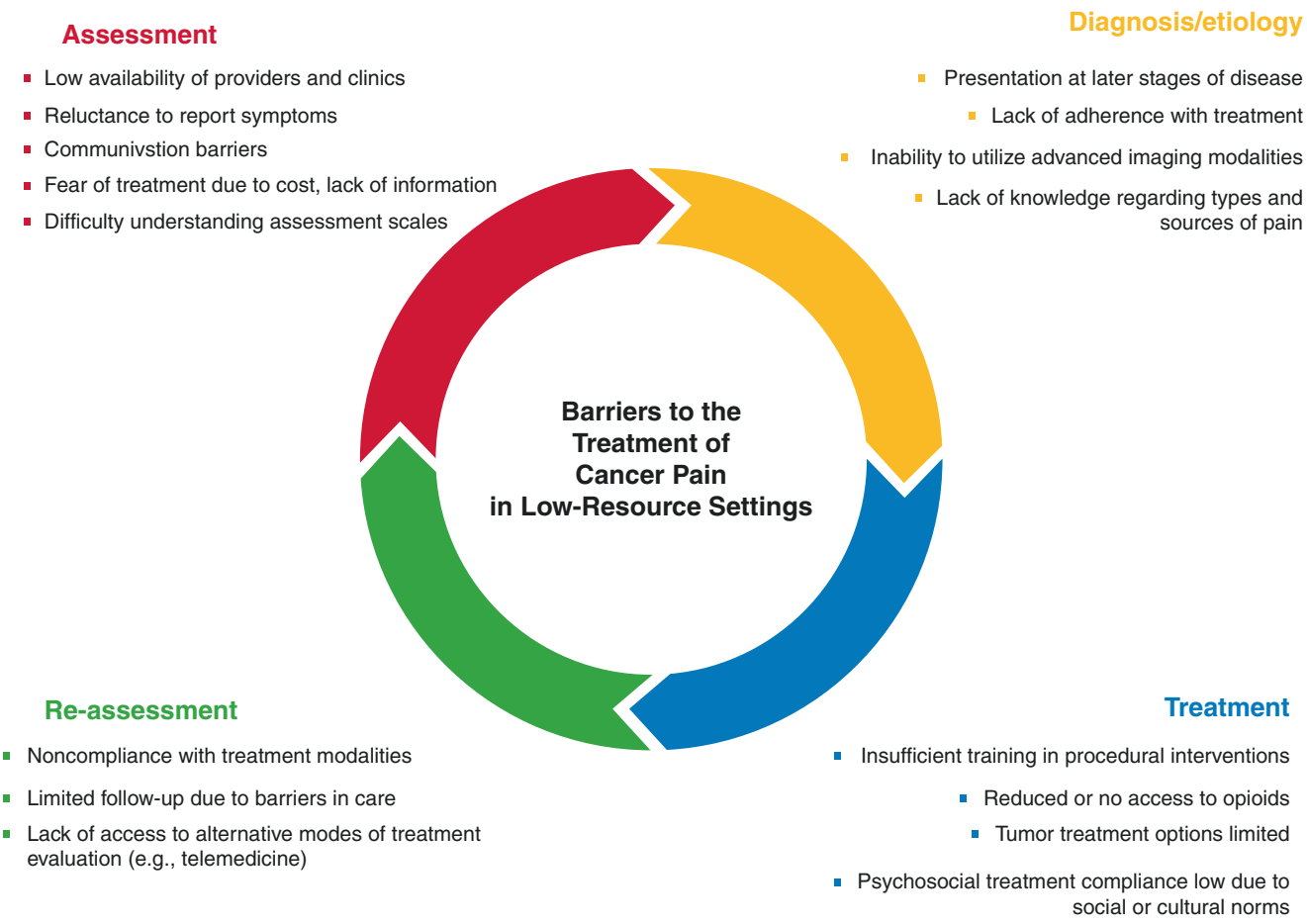

Fig. 67.1 Barriers to the treatment of cancer pain in low-resource settings

(neuropathic). The majority of cancer pain is directly attributable to tumor burden, with other causes being treatment-related or non-cancer-related [13].

Somatic Nociceptive Pain

Pain related to tissue damage is often described as achy or throbbing. This type of pain is often well localized. It can come from a variety of tissues including skin, muscle, and other types of soft tissue. This is the most common type of pain in cancer patients. Oftentimes, it is due to bony disease or metastases [14]. Somatic nociceptive pain generators include various tumor-related sites. This can be from bony disease including primary bone tumors, bone marrow expansion in hematologic malignancies, and bony metastases (e.g., vertebral body metastasis from prostate cancer). Spinal pain can manifest from tumor burden in the vertebral body, bony destruction, vertebral body fractures, and/or spinal cord compression. Soft tissue tumors lead to various pain types at the site of the tumor, including facial pain, headaches, and pleural pain. Further pain etiologies include paraneoplastic pain syndromes such as osteomalacia, osteoarthropathy, and myalgias.

Visceral Nociceptive Pain

In contrast to somatic nociceptive pain, visceral nociceptive pain is often poorly localized. Depending on which organ is affected, it can also be referred to different regions in the body. The characteristics of visceral pain can include a distended feeling and a generalized, dull pain. For example, pain in the myocardium is often referred to the upper extremity. Pain in the gallbladder may be referred to the shoulder. Pain in the ureter may be referred to the lower quadrant. Any organ can be affected but more common sources of visceral pain include hepatic metastases, intestinal obstruction, or venous distension due to tumor burden [15]. Visceral nociceptive pain generators include various syndromes and can result from hepatic distension, intestinal distension, and/or obstruction, peritoneal carcinomatosis, perineal pain, adrenal pain, and ureteral obstruction.

Neuropathic Pain

This third type of pain arises from cancer or cancer treatment affecting the nervous system. This can result in nerve irritation or damage. Abnormal nerve firing may result in dysesthesias, allodynia, hyperesthesias, hypoesthesias, and anesthesia dolorosa. This type of pain is often described as burning, shocking, or lancinating. Neuropathic pain can result from a direct nerve insult (e.g., a tumor compressing a nerve) or inflammatory mediators from adjacent soft tissue destruction. Certain cancer treatments may lead to neuropathic pain states as well, such as chemotherapy-induced peripheral neuropathy or radiation neuritis. Furthermore, surgical treatment of tumors can lead to pain states such as phantom limb syndrome [16]. Certain treatments may also lead to other pain-causing disease states to manifest themselves, such as immunosuppression from chemotherapy leading to post-herpetic neuralgia and subsequent neuropathic pain. Other painful neuropathic states can include leptomeningeal metastases, glossopharyngeal neuralgia, trigeminal neuralgia, various plexopathies (cervical, brachial, lumbar, etc.), peripheral mononeuropathy, malignant radiculopathy, and paraneoplastic sensory neuropathy [17].

Challenges and Opportunities for Cancer Pain Management

The low-resource setting provides numerous challenges and opportunities in the setting of treating cancer pain. The best approach may be to analyze the usual goals and approach for the treatment of cancer pain and then consider the challenges that are presented in a low-resource setting. At that point, the opportunities to optimize care can be elucidated.

The first goal in treatment should be accurate assessment of pain. This can be quite challenging at baseline due to, as previously mentioned, the complex interaction of disease burden, treatment effects, and pain management interventions [18]. Also at play is the fact that non-cancer-related pain etiologies have been reportedly involved in as high as 9% of pain diagnoses [19]. The practitioner should have the patient characterize the pain. This can include temporal features, intensity, quality, relieving and precipitating factors, location, and radiation. Even this simple assessment presents a challenge in the low-resource setting. Due to lack of education, descriptors of pain may be limited. In some settings, lower literacy rates can severely affect accurate assessment. Using functional scales such as the complex disability indices can prove difficult. Lack of trust between certain populations and healthcare workers can lead to inaccurate reporting of pain. This has been reported with indigenous people [20]. An additional confounding factor in determining the etiology of pain in the setting of cancer in low-resource settings is the lack of education and subsequent differences in expectations between the patient, family, and healthcare providers. Communication is essential in order to optimize treatment [21]. The opportunities presented here are self-evident. Increased education to the public can improve communication between patients and healthcare workers. This can also help build trust between the two. Successful public marketing campaigns aimed at improving the image of the health-

care system in general should be a goal. If available, utilizing local trusted figures or champions can help bridge the gap between patients and healthcare workers. Healthcare workers should be well educated in regional differences in social norms, cultural beliefs, and patient-family expectations so that there is not a disconnect when planning the goals of care.

Next, the practitioner should understand the nature of the pain. This not only includes the cause but also the relationship to the pathophysiology of the related cancer or cancer treatment and any associated syndromic features. This presents a challenge as many of these patients may have not undergone appropriate testing due to lack of equipment or financial issues. For example, if a tumor-related vertebral compression fracture is suspected but the area in which the patient and healthcare worker reside does not have access to advanced imaging such as magnetic resonance or computed tomography, the diagnosis cannot be confirmed and treatment may be indefinitely delayed. This is further complicated by the fact that many patients in low-resource settings present at later stages of disease. It has been shown that lower- and middle-income countries have higher mortality rates, leading to significant cancer survival gaps. This is oftentimes due to diagnosis at a later stage and lack of access to prompt treatment (Fig. 67.2) [20, 22].

The challenges here are more systemic in nature and, therefore, more difficult to address. Access to early diagnosis necessitates earlier access to care. This could mean higher numbers of available clinicians to make the diagnosis as well as more healthcare facilities in which to assess, diagnose, and treat a larger number of patients. This also entails facilities with more advanced imaging modalities with which to diagnose patients. Local healthcare workers would also require more nuanced education on the assessment and treatment of cancer and cancer pain. Unfortunately, implementing a large-scale change such as this requires significant funding. Public financing plays a crucial role in this type of implementation. In high-income countries, this type of funding is what has led to modern, sustainable healthcare infrastructures. In most of these countries, universal healthcare is now also standard, leading to increased access to care and health equity across the population. Aid to low- and middle-income countries by countries with higher GDP has been critical in maintaining access to healthcare. However, as income in countries providing aid has increased, the proportion of aid provided, sadly, has not (Fig. 67.3) [3].

Additional challenges in this realm include appropriate access to cancer treatment modalities. Stereotactic radiotherapy, for example, may not be available in a low-resource setting. However, this type of therapy is ideal in some scenarios, such as localized bone tumors [23]. Again, the primary opportunity here comes at great financial cost. Public funding campaigns may be utilized to help fund improvements in cancer treatment modalities. Additional aid from other countries can be sought as well. Some have suggested greater debt relief to low- and middle-income countries so that they can use their government income to improve healthcare infrastructure. Generalized improvements in government infrastructure and strengthened internal tax capacity are systematic improvements that may eventually lead to benefits in the healthcare system.

Once the underlying cause of pain is elucidated, its effects on the patient's quality of life and psychosocial well-being should also be determined and addressed. This can include effects on activities of daily living, physical functioning and capacity, mood, coping, stress levels, familial effects, social interactions, sleep quality, and sexual function. This also ties in with general psychiatric well-being, including anxiety and

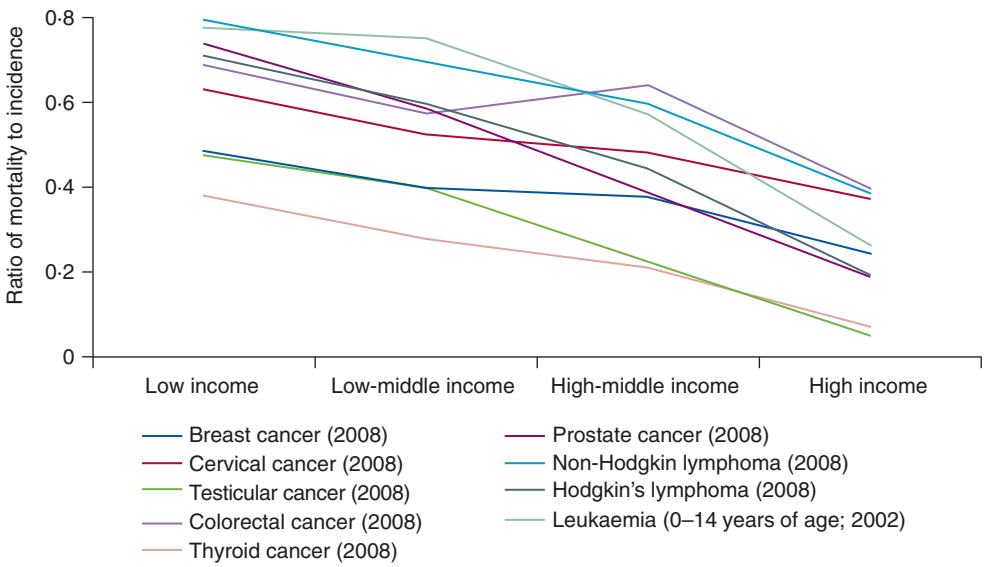

Fig. 67.2 Ratio of mortality to incidence in a specific year by cancer type and country income. People with cancer who live in higher-income countries are often less likely to die from their cancer, compared to people who live in lower-income countries. (From Farmer et al. [22], reprinted from the Lancet with permission Elsevier)

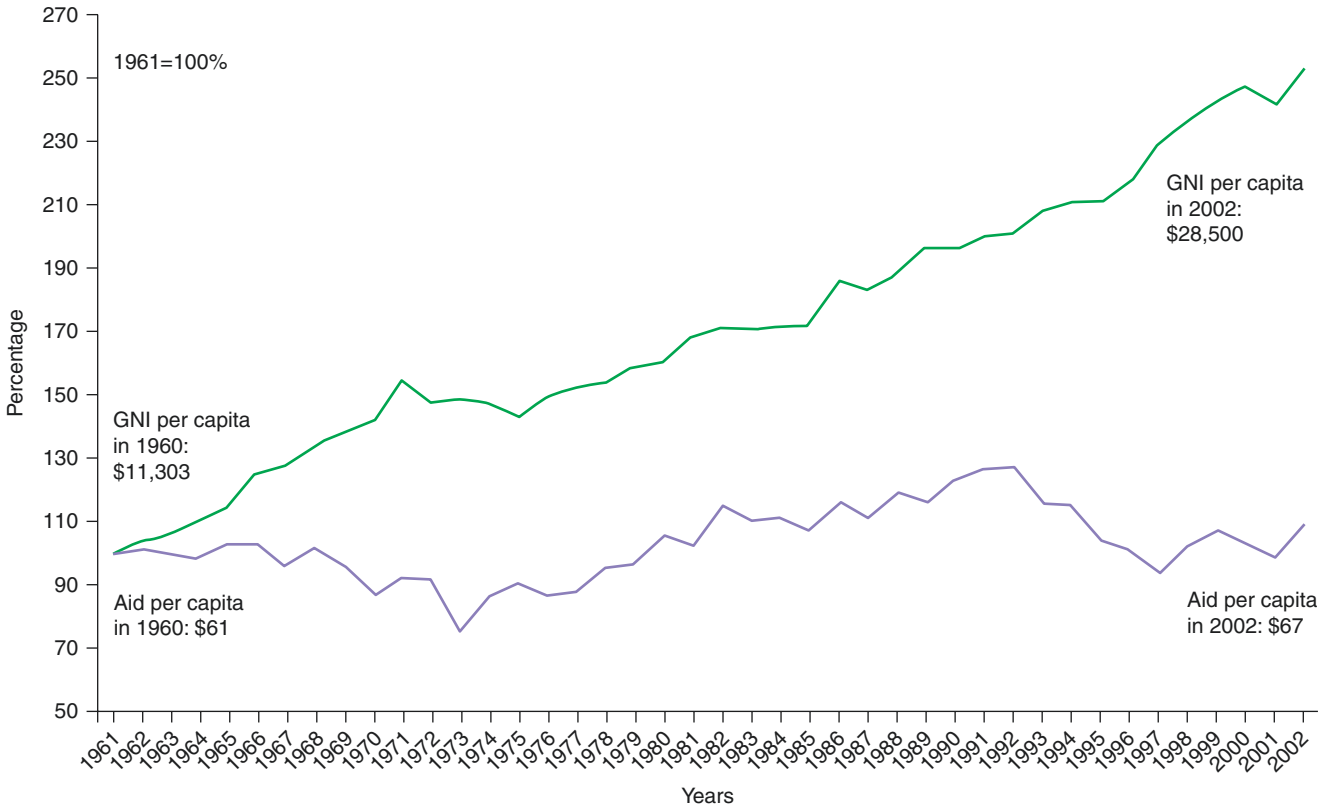

Fig. 67.3 The growing gap: per capita aid from donor countries relative to per capita wealth, 1960–2000. Calculated in $US at 1998 prices and exchange rates. GNI = gross national income. (From Marmot, et al. [3], with permission Elsevier)

depression. Assessment of substance use disorders, personality disorders, and spiritual well-being should also be carried out. This is an area that can prove quite challenging in low-resource settings. Due to lack of education, a cancer diagnosis often carries a stigma and inherent fear factor. There have been reported cases of patients believing it is contagious [24], leading to the patient hiding the diagnosis so that they are not shunned by the community. This, of course, leads to a lack of care until the disease is at a late stage or, in more severe cases, until the patient has passed away from the disease.

Once an accurate diagnosis is made, the treatment plan can begin to be formulated. In an ideal setting, this involves a multidisciplinary team that focuses their efforts on treating the patient, disease process, and symptoms such as pain at the same time. This team can include, but is certainly not limited to, an oncologist to treat the disease of cancer, an internist to treat other underlying medical comorbidities, a psychiatrist to treat coexisting anxiety and/or depression, a physiatrist to coordinate rehabilitative modalities, a pain specialist to perform interventional procedures and optimize pain medication regimens, a radiation oncologist to evaluate for therapeutic radiotherapy, a pharmacist to monitor for medication optimization and interactions, a nutritionist to plan an ideal diet for health and recovery, and even a palliative medicine specialist or hospice physician in cases of end-stage disease. Coordinating such a large team requires considerable resources, which may not be available in limited or low-resource settings. Challenges in these scenarios involve not only availability of specialists, but education in general. Due to limited resources, healthcare providers in these settings may have to play the role of many of these specialists. However, they may lack the education to properly execute these roles. In some cases, the education may be extremely superficial; in others, it may be absent altogether. Opportunities to improve education are vast but require significant long-term commitment from the institutions in that specific infrastructure. There is no short-term solution or "band-aid" for appropriate training. In fact, rushed training may lead to inaccurate diagnoses and improper treatment decisions, leading to patient harm. Appropriate training may require outsourcing, at least on a temporary basis, until educational institutions can provide appropriate teaching and mentorship for trainees.

An additional area which requires education for both the healthcare provider and the patient population is palliative and hospice care. The challenges and opportunities surrounding healthcare provider training are covered above. From the patient population perspective, there are many myths and stigmas present regarding end-of-life care. These

may be tied to certain religious or spiritual beliefs. For example, fatalism (the belief that events in life are predetermined) can lead patients and their families to forego treatment, even at the end stages of disease, because they believe what is transpiring is "meant to be." This can lead to suffering from multiple untreated or undertreated symptoms, including pain. At the end of life, all patients deserve to have the best quality of life they can be given. This requires debunking these myths and removing the stigmas surrounding cancer in many low-resource settings. Many campaigns focus on the word "cancer" and exposing the public to it so that it is not a taboo word or diagnosis. Exposing the community to patients who are cancer survivors is also crucial to show the community that cancer is survivable with appropriate diagnosis and treatment. Using local, well-known figures is an effective method to increase exposure and improve education about cancer diagnosis and treatment.

Managing Cancer Pain

Part of the treatment plan centers around appropriate, multimodal pain management. This includes pharmacologic management, including opioids as clinically indicated, non-pharmacologic management, and interventional procedures. Disease-modifying treatments such as chemotherapy and radiotherapy can significantly affect the patient's pain. However, covering the details of these treatments is beyond the scope of the current chapter. Briefly, these treatments can be considered part of the pain management plan if their administration has a viable chance of reducing tumor burden and thereby reducing the effects of pain by the tumor. Of course, these treatments are not without contraindications and adverse effects. Formulating a plan to treat pain with disease-modifying treatments requires careful coordination between the pain specialist, oncologist, and radiation oncologist.

Non-opioid Pharmacologic Management

The World Health Organization released the cancer pain ladder as a schematic for the basis of cancer pain treatment almost 35 years ago. At the first step of the ladder is non-opioid pharmacologic management. This can include non-steroidal anti-inflammatories and acetaminophen. Non-steroidal anti-inflammatories have been shown to be particularly effective for bony pain from primary or metastatic tumors. This can also be applied to osteolytic lesions. These modalities can also be combined with opioid treatment, although the combination may not be necessarily more effective than opioid monotherapy [25].

These therapies have the benefit of being widely available, even in low-resource settings. However, they come with significant risks. Acetaminophen carries an inherent risk of hepatotoxicity and must be used with caution in patients with compromised liver function. In low-resource settings, one unique consideration is the undertreatment of alcoholism. Alcoholism is a common issue in many regions, and treatment requires long-term rehabilitation – an effort which requires substantial community resources [26]. In settings where resources are limited, alcoholism may be undertreated and treatment with any medications which may compromise hepatic function should be prescribed with caution. Non-steroidal anti-inflammatory drugs have their own set of cautions to consider. They can adversely affect the gastrointestinal, renal, and cardiovascular systems [27]. In low-resource settings, patients should be carefully screened for abnormalities in any of these symptoms prior to treatment with non-steroidal anti-inflammatory drugs. As mentioned earlier in the chapter, patients in low-resource settings avoid seeking healthcare for a multitude of reasons. This presents major issues not only with cancer diagnosis and treatment, but with medical comorbidities as well. If a patient delays seeing a healthcare provider for cancer care, it can be assumed that the same patient likely did the same for other medical problems. Undiagnosed or undertreated hypertension, diabetes, renal disease, coronary artery disease, peripheral vascular disease, and peptic ulcer disease may all be present in patients presenting for care. A thorough history and physical and appropriate diagnostic modalities are critical in ensuring these patients will not be harmed if they are prescribed non-steroidal anti-inflammatory drugs. Some of these risks may be mitigated by using a selective cyclooxygenase-2 inhibitor and/or combining treatment with a proton pump inhibitor [28].

Certain adjuvant medications have been effectively used in conjunction with acetaminophen, non-steroidal anti-inflammatory drugs, and opioids. These adjuvants consist of a variety of classes of medications and treat various types of cancer and treatment-related pain. Being non-opioid, their use should be considered in certain low-resource settings in which opioids may be unavailable due to cost, restrictions, or stigmas. Anticonvulsants such as the gabapentinoids (gabapentin and pregabalin) are often used given the high prevalence of neuropathic components in cancer pain. These N-type calcium channel blockers are often well tolerated and widely available. Gabapentin has been in use for decades and is generally available. Pregabalin is newer but is now available in generic form. Other anticonvulsants such as carbamazepine, topiramate, oxcarbazepine, valproate, and lamotrigine may also be used for neuropathic pain. These medications may not be as available as the gabapentinoids and some have the potential for significantly greater

adverse effects. Antidepressants, specifically tricyclics and serotonin-norepinephrine reuptake inhibitors, can be effective in neuropathic cancer pain as well. Many of these medications have been widely available for quite some time as well and have low associated costs. They can be particularly helpful in treatment-related neuropathic pain states such as chemotherapy-induced peripheral neuropathy. Another class of medication are topical adjuvants. This can include lidocaine cream, lidocaine patches, lidocaine liquid, capsaicin cream, capsaicin patches, non-steroidal anti-inflammatory cream, doxepin cream, and doxepin elixir. Although many of these are now available in generic form, any medication with a transdermal application system increases the manufacturing cost. Additionally, a patient may require multiple patches. In a low-resource setting, this may not be ideal for pain that may be chronic or expected to continue for the long term. For bone pain, glucocorticoids, bisphosphonates, and calcitonin are often used. Glucocorticoids have a host of adverse effects, especially with long-term use, and should be used with caution. Additionally, their use should be coordinated with the treating oncologist due to risk of immunosuppression. Bisphosphonates are considered generally safe, although there is a risk of osteonecrosis and renal injury. These concerns should be addressed with a careful history and physical examination, the challenges of which are outlined above [29].

Opioid Pharmacologic Management

Opioids remain the mainstay of treatment of cancer pain, particularly in advanced stages of disease. They have significant risks associated, including respiratory depression, nausea, constipation, pruritus, etc. The risk of respiratory depression remains the biggest clinical concern, as this can be life threatening. This risk is compounded by the concurrent use of benzodiazepines. Patients with cancer pain are often prescribed benzodiazepines due to the high incidence of anxiety surrounding a cancer diagnosis as well as cancer treatment. Careful risk stratification is needed to mitigate the risks surrounding opioids. These risks have been highlighted in recent years in the midst of the opioid epidemic. Overuse, misuse, and diversion remain significant concerns in the prescription of opioid analgesics [30]. Patients should undergo a risk assessment before beginning treatment with opioids. This can help identify high-risk patients and guide the clinician in appropriate prescribing for a particular patient. Consistent reassessment should be performed, as patients can shift between risk stratification categories over time. Additionally, patient education is critical when it comes to opioid management. Tempering expectations and explaining the risks of opioid use as well as the differences between addiction, physical dependence, and tolerance are vital in maintaining a healthy provider-patient relationship, especially in the setting of chronic opioid use. Monitoring patients consistently for appropriate outcomes is also important to ensure that the medication prescribed is helping them achieve their goals and outcomes. Outside of arbitrary pain scores such as the visual analogue scale, functional outcome measures should be utilized. Examples include the Short-Form 36, the Brief Pain Inventory, and the Patient Global Impression of Change [31].

Selection of opioids remains largely dependent on regional availability and clinical familiarity and training. Pure mu-opioid agonists remain the most commonly used and available. Initial selection will also depend on the severity of pain and the patient's tolerance to opioid agonists. In opioid naive patients, a starting point may include tramadol, a weak mu-opioid agonist with serotonin-norepinephrine reuptake inhibition effects or codeine. Tramadol's unique mechanism of action may make it more suitable for patients with a larger component of neuropathic pain. Caution should be used in those patients with renal dysfunction or those who are prone to seizures, as tramadol can reduce the seizure threshold. Codeine's mechanism of action relies on its conversion to morphine. In certain patient populations, hypermetabolism of codeine may lead to potentially toxic doses of morphine [32]. In the next tier of opioids, hydrocodone is most commonly available in North America and, to a lesser extent, in Europe. The immediate-release form is paired with acetaminophen (now limited in the United States to 325 mg acetaminophen per tablet), and the newer extended release form is hydrocodone without any paired medications. Caution should be used, as mentioned previously, with acetaminophen use. The extended release form is newer and currently brand name only, signifying that it is a higher cost and may be more difficult to obtain. In low- and middle-income countries, hydrocodone is scarcely available. Other opioid options include oxycodone, oxymorphone, morphine, and hydromorphone. Each of these is available in short acting, as well as long-acting, formulations. If cancer pain is continuous, a long-acting formulation is preferred with an immediate-release formulation given additionally for breakthrough pain. Caution should be used with hepatic dysfunction in any of these medications, but particularly with morphine due to accumulation of its metabolites [33]. Fentanyl is a potent opioid most commonly available as a transdermal patch for long-acting analgesia. It is also now available in a transmucosal formulation for rapid onset action. However, due to its unique routes of administration, manufacturing costs cause the cost to the patient to oftentimes be higher than other opioids. This is particularly problematic in low-resource settings. Availability of fentanyl products may also be an issue, although the transdermal fentanyl patch has been used long enough now that it is widely available. Methadone is a unique opioid agonist that also has an effect on the N-methyl-D-aspartate receptor. This medication has a long and variable half-life, which can be helpful in

continuous pain but may also pose an issue if it is to be discontinued as it persists in the system for an extended period of time. Its NMDA activity is beneficial when treating pain with a neuropathic component. It also lacks active metabolites, making it relatively safer for those patients with renal dysfunction. It does carry unique considerations, including the potential for QT interval prolongation. This should be monitored closely in order to prevent risk of torsades de pointes. Another issue is the stigma associated with its use. Since it is used in rehabilitative programs for opioid addiction, patients may be hesitant to use it for their cancer pain. In the low-resource setting, stigma with opioid use is already a major issue and the additional stigma with methadone may cause patients to decline treatment with it.

In the cancer pain population, routes of administration of opioids play an important role in treatment. Many types of cancer and cancer treatment may affect gastrointestinal absorption, leading to inadequate analgesia with oral opioids. Consideration should also be given to opioid metabolism and accumulation of metabolites in those patients whose hepatic and renal systems may be affected by disease or treatment. Patients undergoing multiple surgeries may be nil per os frequently, necessitating the use of alternative routes of administration such as intravenous, transdermal, or mucosal. Adjustments in doses may need to be frequent and require timely reassessment. When changing doses, several days may need to elapse for steady state blood concentrations to change with long-acting opioids. This may be up to 1 week in the case of a unique medication such as methadone.

Management of side effects is also crucial in opioid treatment for cancer pain. Opioid induced constipation remains a major issue for many patients, so much so that they may want to decrease doses in order to improve this side effect. Dietary adjustments and over-the-counter stool softeners and stimulant laxatives may be used in mild cases. Peripheral opioid antagonists such as naloxegol may be used for more severe cases. Opioid antagonists such as methylnaltrexone and naloxone may also be considered in select cases. Unfortunately, the availability of these antagonists is highly variable, especially in low- and middle-income countries. Other side effects to consider include mental clouding, somnolence, pruritus, nausea, and urinary retention. These can normally be ameliorated by dose adjustment and adjuvant treatment (e.g., a stimulant for mental clouding and a 5-HT3 antagonist for nausea).

Opioid Consumption in Low- and Middle-Income Countries

Despite significant data indicating that cancer pain continues to be often undertreated, there remain significant barriers in treatment of pain in low-resource settings such as low- and middle-income countries. The barriers to appropriate care are numerous and include low priorities given to pain relief. Additionally, national guidelines on pain treatment are often lacking or outdated. This is accompanied by social stigmas surrounding cancer, cancer treatment, and cancer pain, as highlighted previously in this chapter. On the topic of opioids, availability remains the major issue. This may be due to governmental restrictions on the import of opioids as well as restrictions on use due to fear of misuse, overuse, addiction, and diversion [34]. Policy issues causing decreased availability include lacking national guidelines on opioid imports, tight regulations on import and use due to fear of misuse and cultural beliefs and/or stigmas, and inadequate health governance. Clinical barriers to opioid use include lack of prescribers, lack of education in the healthcare worker community as well as the patient population, stigma and fear, and limited number of clinics available to see the appropriate number of patients and spend enough time with them for opioid education. Systemic resource issues also contribute and may include lack of resources to store and appropriately distribute opioids, low or absent numbers of pharmacies (especially in rural regions), and inconsistent stock.

As morphine equivalents remain the standard by which all opioids are judged, global consumption via morphine equivalents is a metric used by the World Health Organization to study global opioid use (Fig. 67.4) [35].

Low- and middle-income countries accounted for 84% of the world's population in 2018 [36]. The disparity in availability of morphine and other opioids in relation to patients in need is highlighted in the map above, from a report in The Lancet Commissions. This figure is a dismal reminder of the glaring disparity between high-income and low−/middle-income countries. In the United States, Canada, and Western Europe, the population remains over-served by at least hundreds of percentage points greater than their need. In low- and middle-income countries, the population remains underserved usually below 15% and even below 1% in some countries. In addition to the systemic issue related to opioid use in low- and middle-income countries, one additional issue remains inconsistent availability of a medication that a patient may be currently using. Month to month, stock changes may require clinicians to alter the medication used. For example, a patient may be stable on transdermal fentanyl for 3 months, and, the following month, the country no longer has that medication available. Although opioid rotation is an established practice, it is often a slow and inaccurate process and may lead to periods of uncontrolled pain. This is especially troublesome when applied to a patient who was doing well on one medication but now has to switch to one which may be less ideal because the country where they reside does not have policies or procedures in place for stable stocks of medications.

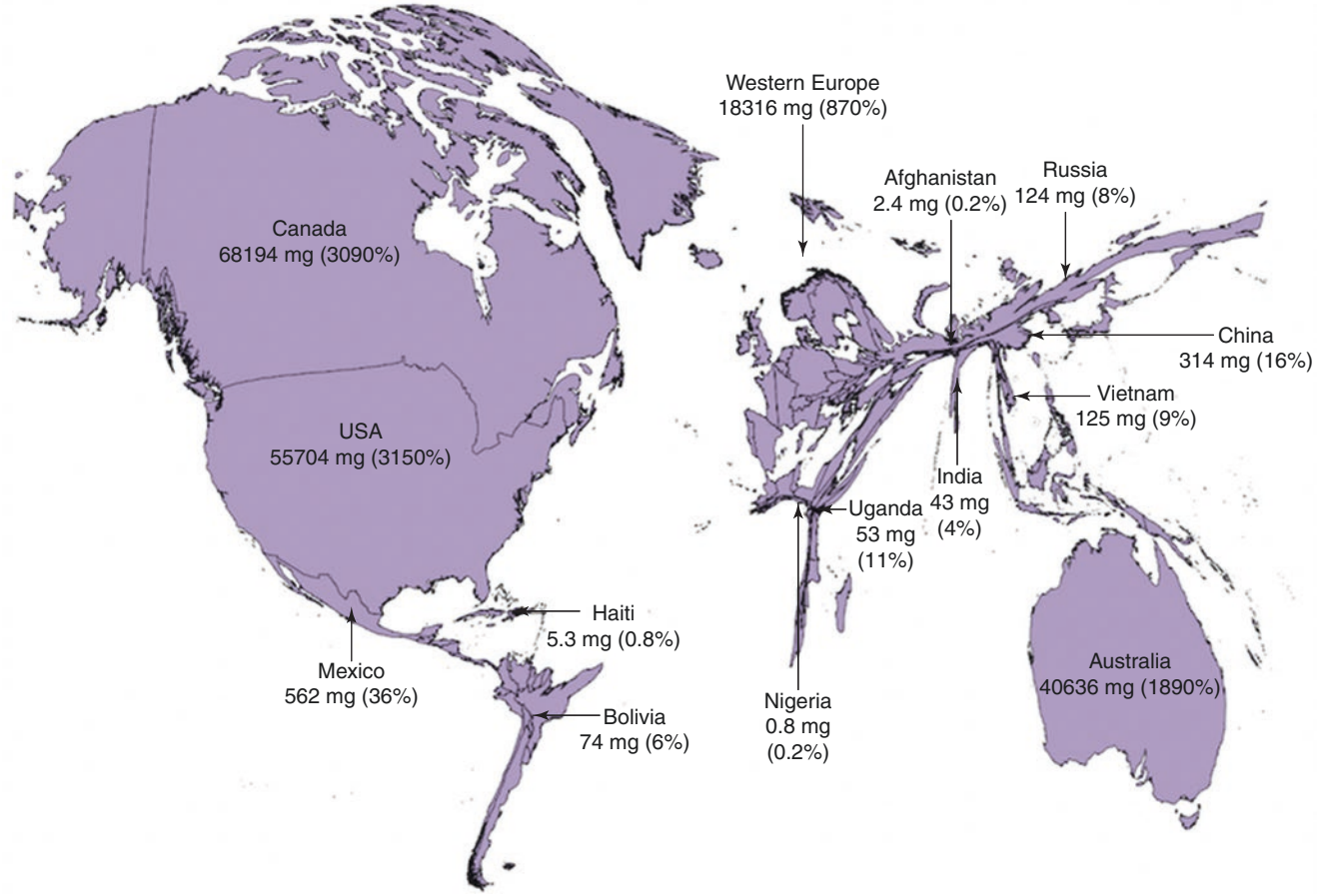

Fig. 67.4 Distributed opioid morphine equivalent (morphine in mg/patient in need of palliative care, average 2010–2013) and estimated percentage of need that is met for the health conditions most associated with serious health-related suffering. Source: International Narcotics Control Board and WHO Global Health Estimates, 2015. (From Knaul, et al. [35], with permission Elsevier)

Non-pharmacologic Management

Non-pharmacologic, non-interventional treatments for cancer pain are becoming more commonly used as they offer potential benefits with minimal side effects. This can include psychotherapy, physical therapy, and acupuncture. This category also encompasses programs which may assist with associated components of cancer pain such as pain education, support groups, family stress changes requiring therapy, financial programs to assist with pharmacologic or interventional treatments for pain, etc. Disparities in low-resource settings can significantly affect response to these treatments. One study has shown a favorable response to patient coaching in the management of cancer pain in ethnic minorities [37]. Educational programs are critical in reducing disparities between groups in low-resource settings. As previously mentioned, lack of education leads to propagation of myths and stigmas which delay care and lead to diagnosis in later stages of disease with greater disease-related suffering. Dispelling myths surrounding physical manipulation methods such as physical therapy and acupuncture is also vital, as these modalities can significantly improve functionality in cancer pain patients. Family counseling is also an important component of cancer pain treatment, especially when approaching the end of life and with involvement of palliative care.

Interventional Procedures

Interventional procedures can play a crucial role in the treatment of cancer pain. As pain interventions have advanced, practitioners have been able to perform more advanced procedures without increasing the invasiveness of these procedures. The types of procedures performed depend on an accurate diagnosis of the underlying cause of pain. Special consideration must be given to any areas surrounding a tumor or metastases, given that these areas are highly vascular and the risk for bleeding may be increased. Additionally, consideration must be given to the patient's oncologic treatments, as certain therapies may interfere with clotting ability and wound healing. The use of corticosteroids must also

carefully be weighed with the cons of such medications, especially on a repeated basis.

For head and neck tumors, peripheral nerve blockade is available as a treatment modality to assist with pain management. Examples of such blocks include trigeminal nerve blocks, stellate ganglion blocks, occipital nerve blocks, and cervical nerve root blocks and/or epidural steroid injections. For upper and lower extremity tumors, somatic nerve blockade can provide temporary relief or pain management surrounding surgical resection. Sympathetically mediated pain can be treated using stellate ganglion or lumbar sympathetic blocks. Post-surgical syndromes such as post-mastectomy pain syndrome and post-thoracotomy pain syndrome can be treated with peripheral nerve blockade, such as intercostal nerve blocks. Splanchnic nerve or celiac plexus blockade (and ablation) is commonly used for visceral abdominal pain. Similarly, superior hypogastric plexus blockade (and ablation) can be used for visceral pelvic pain. Pain at the perineum and rectum can be treated by blocking the distal end of the sympathetic chain, at the ganglion impar.

More advanced therapies include vertebral augmentation, which is used to treat tumor or osteoporosis-related vertebral compression fractures. Newer technologies allow for radiofrequency ablation of tumor sites in the vertebral body prior to polymethylmethacrylate injection. Implantable therapies such as dorsal column stimulation and intrathecal drug delivery systems are available as well. In cancer pain, intrathecal drug delivery systems allow for the use of intrathecal opioids to effectively treat pain while lowering some adverse effects of oral or transdermal opioids. For severe, refractory cases of pain, advanced functional neurosurgical techniques such as cordotomy can be employed.

Most of these interventions are performed under image guidance—commonly fluoroscopy or ultrasound. Computed tomography guidance may be used in select cases.

Barriers to the use of interventional techniques remain present in low-resource settings. The setting and equipment needed to perform such interventions may not be readily available. The cost to set up a procedure suite to perform these interventions is much higher than that of acquiring most pharmacologic treatments. Additionally, the training required for the practitioner remains substantial. Specialists who can perform such procedures may not be readily available in low-resource settings, and systematic infrastructure changes will need to be implemented before this issue can be resolved.

Recommendations

In order to overcome barriers in care in low-resource settings, several changes can be undertaken in a systematic, stepwise fashion in order to improve access to care. The first place to begin is changes in policy. This can occur on a local, regional, and national level. Policies need to be in place to improve access to care for cancer pain patients. This includes dedicating resources, financial and otherwise, to the development of appropriate healthcare facilities, training of healthcare personnel, advocating to local and national community leaders, and working with national and international groups in order to implement these policies. These groups and organizations can be small, local focus groups or large, international organizations such as the Pain & Policy Studies Group [38]. These policies need to be aimed at increasing availability of care for cancer pain patients and avoiding restrictions usually placed on issues such as opioid importing and regulations.

Availability of pharmacologic treatments is another area that is high yield in terms of increasing care to cancer pain patients. In addition to the policy changes mentioned above, infrastructure needs to be put in place to obtain, store, and properly dispense medications to alleviate pain and suffering. This includes having licensed healthcare providers who are well trained in these treatments and are able to dispense them to patients appropriately. Consistency also needs to be maintained on medication stocks so that fluctuations do not occur regularly. In countries with tight regulations on opioids in particular, exceptions should be made for those suffering from cancer pain so their treatment is not delayed or prevented.

Improving education is critical in improving care for these patients. This applies to both healthcare workers and the population in general. In regard to healthcare workers, they need to be familiar with the tenets of cancer pain treatment and feel comfortable applying principles commonly used as the standard of care around the world. There also need to be enough healthcare workers so that a small number do not get overwhelmed by a large patient-to-healthcare worker ratio. A high ratio can lead to inadequate time with the patient, increasing the potential for misdiagnosis and inappropriate treatment choices. An example of healthcare worker education occurred in Uganda, with the 9-month Clinical Palliative Care Course. This course allowed clinicians to learn the basics of palliative care in 9 months, thereby greatly increasing access to care for their patients [39]. Educating the public is also crucial in order to debunk any myths and remove stigmas associated with cancer. This will allow earlier access to care and more effective treatments to take place. Local community leaders should be involved in advocacy and education campaigns. Cancer survivors should be highlighted so that the community can see cancer as a treatable diagnosis, instead of one that always leads to mortality.

Implementation of these recommendations can be challenging and requires coordination between healthcare providers, local leaders, and government figures. It also takes

time to implement such changes, but even on a small scale, the benefits can be seen. Beginning with a few goal-oriented tasks (e.g., leading a community campaign to improve education about breast cancer on a local level and implementing policy changes to remove restrictions on morphine prescribing for cancer pain patients on a national level) can yield palpable results that can affect patient outcomes. Broader changes, such as strengthened tax capacity in order to improve healthcare budgets to build more facilities to improve access to care, certainly take more time but are part of the ultimate goal.

Conclusions

Low-resource settings provide unique challenges and opportunities in the treatment of cancer pain patients. One must start with the basics of assessment of cancer pain, including a detailed understanding of the etiologies of cancer pain. The types of cancer pain include somatic nociceptive, visceral nociceptive, and neuropathic pain. These can be affected by cancer disease states in a variety of ways including direct tumor-related pain, mass effect on structures adjacent to the tumor, destruction of tissues surrounding the tumor, and paraneoplastic pain syndromes. Treatment of cancer can also lead to certain pain states such as chemotherapy-induced peripheral neuropathy. Appropriate diagnosis leads to an effective treatment choice. The WHO ladder begins the first step of treatment with non-opioid pharmacologics and adjuvant medications, then moves on to the next step of opioid treatment for increasing or refractory pain. Interventional treatment modalities also play a critical role in effective cancer pain management. These may range from guided nerve blocks to implantable therapies such as intrathecal drug delivery.

The challenges presented in low-resource settings begin before the patient even presents. Prejudices against the healthcare system cause patients to avoid care or seek alternate care until their disease is at a more advanced state. This leads to a significantly more complex pain picture on initial presentation. Many treatment modalities that could have been utilized at an earlier state may now not be appropriate in such cases. Increasing public education in order to improve trust between the community and the healthcare system can ameliorate this issue. Healthcare providers must present a unified message with local, regional, and national leaders.

As the patient continues on his or her treatment journey, limited resources may adversely affect proper diagnosis and treatment. Modalities such as advanced imaging and modern therapies may not be available in low-resource settings, leading to poor treatment options for cancer patients. The opportunities here are more difficult to seize, as many of these issues are related to systemic issues such as lack of financial support and governmental restrictions. Improvements to access of care will require longer-term solutions such as increased external aid and changes in local, regional, and national policies. This will allow improvement in healthcare infrastructure, which is necessary in order to provide better care to patients. Included in such improvements are a larger number of treatment centers, advanced imaging equipment, and better training for healthcare personnel. Medication availability to treat cancer pain is also highly variable in low-resource settings. This is linked to both financial support and strict laws in regard to opioids in certain countries. Unfortunately, this often leads to undertreatment of cancer pain as patients may not have access to the opioids they need; even if they do get access, it may be temporary as supplies are often inconsistent. There are many opportunities here to improve access to care, but again they require systemic changes such as improved funding and changes in the country's laws.

Many of the recommendations in this chapter take significant time, effort, and resources to implement. However, even small-scale changes can make significant differences in cancer pain patients' quality of life and outcomes. Low-resource settings provide settings in which the effects of these smaller-scale improvements can provide relatively significant effects.

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Curriculum Development

68

Angela B. Creditt and Kevin Sing

In the United States, overall cancer incidence has been relatively stable over the last decade, ranging from 400 to 500 cases per 100,000 individuals [1]. Cancer death rates, however, have dropped by 29% from 1991 to 2017 as significant therapeutic advances have been achieved. Major developments in precision medicine, immunotherapies, and targeted therapies occur on a yearly basis, revolutionizing the delivery of oncologic care. For example, the 5-year overall survival of advanced melanoma in the interleukin era was 5–10%; with the combination of nivolumab and ipilimumab, that number has reached over 50% [2]. Thus, while disease-specific oncologic emergencies continue to occur, providers now contend with an array of new medications, as well as the life-threatening toxicities they can bring.

The development of new treatment strategies and a subsequently declining mortality rate has resulted in an increased number of visits to the emergency department (ED). In fact, most cancer patients will seek urgent care at least once during the course of their disease. Additionally, almost 60% of cancer patients who receive care in the ED will be admitted to the hospital [3]. Depending on hospital protocols and bed capacity, hospitalists may often assume the role of primary provider for cancer patients with hematology-oncologic physicians consulting to assist with management and treatment. Given the various specialties that will participate in the care of these patients, it is imperative that physicians receive thorough education on the identification and treatment of acute, and potentially life-threatening, oncologic morbidities.

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Development of an Oncologic Emergency Medicine Curriculum

Medical students, residents, fellows, practicing physicians, and advanced practice providers – all have the potential to provide care to cancer patients, all can affect the outcome of these patients, and all will benefit from education on oncologic emergencies. However, each requires a different fund of knowledge and different educational approach. Undergraduate and postgraduate medical curricula must address core clinical competencies [4], but they are unique to each group of learners. For example, resident education is tailored toward milestones (on knowledge, clinical skills, attitudes, and other attributes) outlined by the Accreditation Council for Graduate Medical Education (ACGME) and the American Board of Emergency Medicine (ABEM) [5]. Here we will discuss and outline curriculum development as it pertains to an emergency medicine residency program. From this, adjustments can be made based on institutional differences or for other residency programs that will benefit from learning more about oncologic emergencies, such as internal medicine and family medicine. The second half of this chapter discusses special considerations for undergraduate medical education, hematology-oncologic fellowships, and continuing medical education.

Emergency Medicine Residency

Problem Identification and General Needs Assessment

Adult (age ≥ 18 years) cancer-related visits to the ED have been increasing; there were 3.3 million visits in 2006 and 4.8 million in 2012. 4.2% of all adult ED visits in the United States were made by a patient with a cancer diagnosis, and this number is likely higher in facilities with an associated cancer treatment center. Furthermore, cancer-related ED visits are more common among older patients and are associated

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with a significantly higher inpatient admission rate (59.7% compared to 16.3% of non-cancer-related visits) [6]. Given the prevalence of cancer-related visits and potential severity of illness, physicians must be prepared to provide high-quality care to these patients, including prompt identification and treatment of disease-specific and therapy-related oncologic emergencies.

Over their postgraduate medical training, emergency medicine residents face the challenging task of mastering a broad base of knowledge encompassing all medical disciplines with a focus on the acutely ill or injured and emergent resuscitation of critically sick patients. Under this umbrella falls oncologic emergencies. The specific topic of oncologic emergencies has few resources dedicated to offering curriculum direction or suggested programs that may guide educators on effective teaching methods. Yet, in 2016, the *Model of the Clinical Practice of Emergency Medicine* (EM Model) added "oncologic emergencies" as a required curricular component requiring residents and practicing emergency physicians to obtain core fundamental knowledge on this subject in order to provide proper treatment and patient care [7]. What the EM Model did not do is provide education objectives or an outline of what content should be covered in the curriculum.

Beyond the EM Model, the ACGME, the body responsible for accrediting all graduate medical training programs, publishes "common program requirements" for each residency and fellowship. Essentially, these requirements are basic standards for the knowledge, skills, and attitudes deemed necessary that residents should acquire to appropriately take care of patients [8]. From this, each specialty has its own document outlining program requirements specific to that discipline. For emergency medicine, it states:

> The curriculum must contain the following educational components: a set of program aims consistent with the Sponsoring Institution's mission, the needs of the community it serves, and the desired distinctive capabilities of its graduates...competency-based goals and objectives for each educational experience designed to promote progress on a trajectory to autonomous practice...a broad range of structured didactic activities.

Additionally, it describes the competencies and milestones, such as professionalism, patient care and procedural skills, medical knowledge, etc. that educators must use to track and evaluate individual residents [9]. While the ACGME program requirements provides a comprehensive curricular foundation, as does the EM Model, it does not provide specific educational objectives or itemized curricular components that should be taught to each learner.

To supplement this, emergency medicine residency programs frequently utilize either *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 9th edition (McGraw-Hill Education/Medical; 2019), or *Rosen's Emergency Medicine*: *Concepts and Clinical Practice*, 9th edition (Elsevier; 2018), as a reference or guideline for educational components. Each textbook includes a section on oncologic emergencies; see Table 68.1 for specific topics covered. Both resources include content on the more commonly known oncologic emergencies, while *Tintinalli's* seems to have a more diverse list of topics. Neither currently discusses newly identified cancer-related emergencies such as immunotherapy toxicities.

Table 68.1 Topics included in emergency medicine textbooks

Textbook and chapter	Conditions discussed
Tintinalli's emergency medicine: A comprehensive study guide Chap. 239, emergency complications of malignancy	Airway obstruction Bone metastases and pathologic fractures Spinal cord compression Malignant pericardial effusion Superior vena cava syndrome Hypercalcemia of malignancy Hyponatremia due to syndrome of inappropriate anti-diuretic hormone (SIADH) Adrenal crisis Tumor lysis syndrome Febrile neutropenia Hyperviscosity syndrome Thromboembolism Nausea and vomiting Extravasation of chemotherapeutic agents
Tintinalli's emergency medicine: A comprehensive study guide Chap. 240, Emergency Complications of Malignancy	Emergencies related to local tumor effects Emergencies related to biochemical derangement Emergencies related to hematologic derangement Emergencies related to therapy
Rosen's emergency medicine: Concepts and clinical practice Chap. 115, Selected Oncologic Emergencies	Febrile neutropenia Metastatic spinal cord compression Malignant pericardial disease Hypercalcemia Tumor lysis syndrome Leukostasis Superior vena cava syndrome

Another core component of emergency medicine in general but also particularly as it relates to patients with cancer is palliative and end-of-life care. The 2016 EM Model notes that clinical knowledge in healthcare coordination, including end-of-life and palliative care, advanced directives, coordination with hospice, and organ donation, is integral to the practice of emergency medicine [7]. Yet, there is a perceived deficit in knowledge of palliative and end-of-life care by emergency residents and physicians [10], and only 59% of residencies have been found to teach these competencies in their program [11]. In part, this could be due to barriers within the ED such as perceived lack of time, lack of experience or expertise among faculty, and lack of faculty interest in palliative care. Additionally, the majority of programs

have access to hospice and palliative medicine consultants, thereby potentially negating opportunities for clinical education [11].

In 2007, a formal curriculum entitled The Education in Palliative and End-of-Life Care for Emergency Medicine (EPEC-EM) was created with the support of the National Institutes of Health. The EPEC-EM was developed by emergency physicians and nurse educators to enhance education in these essential clinical competencies as it specifically relates to the field of emergency medicine. However, despite this initiative, there remains a general lack of formal palliative care training in emergency medicine residency programs across the country. Emergency residents and physicians feel palliative care skills are important and desire more dedicated training in this field [11].

Given the lack of a generalizable detailed emergency medicine curriculum and related literature, it is difficult to define precisely the didactic education residents currently receive on oncologic emergencies. Furthermore, clinical exposure likely varies considerably based on characteristics of the residency program. For example, those who train at an institution with an affiliated cancer treatment center likely see a significantly higher cancer patient population than those without a center. This will ultimately translate to improved clinical experience and knowledge, confidence in workup and diagnosis, and an enhanced ability to manage emergent conditions affecting cancer patients, thereby resulting in higher-quality care and improved patient outcomes.

Goals and Objectives

Based on the problem identified and needs assessment outlined above, the overall goal and specific objectives for an oncologic emergency medicine curriculum can be developed. These objectives will help establish curricular content and learning approaches, help focus the learner, and provide a foundation for evaluation. The overall goal for a curriculum dedicated to oncologic emergencies is to expand and develop resident physician knowledge, clinical skills, and behaviors to effectively diagnose and treat patients who present with an oncologic emergency, thereby improving medical decision making and patient clinical outcomes. Specific objectives include the following:

- Identify and manage emergent medical conditions that occur in cancer patients, including local tumor effects, complications related to cancer treatment, hematologic derangements, and biochemical abnormalities.
- Understand novel cancer therapies, associated side effects, management, and treatment options.
- Exhibit proficient clinical skills through consideration of relevant differential diagnoses, workup, and management based on a cancer patient's medical history and clinical presentation.
- Recognize the following conditions: neutropenic fever, superior vena cava syndrome, tumor lysis syndrome, malignant spinal cord compression, blast crisis, immunotherapy and CAR-T cell toxicities, hypercalcemia, pulmonary embolism, hyperviscosity syndrome, malignant pericardial effusion, bone marrow transplant complications, and radiation therapy complications. See Table 68.2 for a more conclusive list of conditions.
- Learn supportive treatment plans for patients who need symptomatic care (i.e., nausea, vomiting, cancer-related pain, etc.) and understand when to include consultants such as palliative medicine and hematology-oncologic specialists to optimize patient management outside of the ED.
- Demonstrate sensitivity and commitment to ethical principles by assessing goals of care, including advanced care directives, and the patient's emotional state during their ED visit.
- Understand appropriate disposition including: discharge home, admission to the hospital or hospice, and transfer to higher level of care.

Table 68.2 Suggested oncologic emergency medicine educational topics

Local tumor effects	Airway hemorrhage, airway obstruction, bone metastases and pathologic fractures, brain metastases, malignant pericardial effusion, malignant pleural effusion, malignant spinal cord compression, superior vena cava syndrome
Complications related to cancer treatment	Bone marrow transplant complications, chemotherapy adverse effects, extravasation of chemotherapeutic agents, immunotherapy and CAR-T cell toxicities, radiation therapy complications, symptom management (i.e., nausea and vomiting, pain control)
Hematologic derangements	Blast crisis, hyperviscosity syndrome, leukostasis, neutropenic fever, pulmonary embolism
Biochemical abnormalities	Adrenal insufficiency, hypercalcemia, hyponatremia secondary to syndrome of inappropriate anti-diuretic hormone (SIADH), tumor lysis syndrome

Educational Strategies

While every resident has gained a foundation of knowledge in oncologic from medical school, their awareness and understanding of cancer-related emergent conditions may vary considerably (see the section on medical school education later in this chapter). Therefore, to achieve curriculum objectives, appropriate educational content and teaching methods should be selected. Learners can obtain lower-level knowledge through formal lectures, suggested reading

assignments, and asynchronous online modules. Case-based problem-solving exercises and other small group modules, such as simulation, that rely on active participation by learners can then be implemented to enhance clinical reasoning skills. Finally, bedside teaching and on-shift clinical education must occur to cement knowledge learned through didactic instruction.

Ideally, the majority of education will occur during weekly resident conferences in a set educational block dedicated to oncologic-related topics in emergency medicine. The amount of time allotted to this block is dependent on several factors, such as 3- versus 4-year residency programs and how often the didactic curriculum is repeated during a resident's postgraduate education. In general, a minimum of 8 to 10 hours of fundamental oncologic emergency training using variable teaching methods is necessary to enhance knowledge retention. These methods can (and should) include PowerPoint® (Microsoft, Redmond, WA) lectures, small group education including problem- or case-based and team-based learning, simulation and role playing, flipped classroom, and bedside teaching.

Utilizing PowerPoint lectures for a portion of teaching in oncologic emergencies allows for the delivery of concrete, structured information to a large group of people. This provides a knowledge base to residents than can then be augmented using other learning techniques. In particular, small group learning creates high-yield and interactive didactic sessions that yield improved learner engagement, teamwork, clarification of knowledge gaps, and opportunities for resident assessment. Ideally, the small group session would be resident directed with a faculty leader available to answer questions, clarify any points of confusion, provide additional information as needed, and keep the group focused and on track [12].

Small group sessions can be conducted using team-based learning, case-based learning, or simulation/role play. In team-based learning, residents first complete an educational assignment. Subsequently, in conference they are tested on pre-class material via an individual readiness assurance test (iRAT), then a group readiness assurance test (gRAT), followed by a group exercise challenging residents to apply their knowledge to a scenario as a team. A single instructor is required to review learning points and clarify any confusion. Team-based learning has been shown to improve learning outcomes and examination scores as well as communication and teamwork skills [12]. Case-based learning utilizes vignettes of real or hypothetical patients to facilitate a discussion at each decision point. Throughout the case, an instructor asks questions to highlight different learning objectives, such as clinical presentation, development of a differential diagnosis, treatment, etc. This technique can also be used to tackle more challenging objectives within the oncologic emergency medicine curriculum, such as communication with a patient and/or their family or discussions on goals of care and do-not-resuscitate orders [13]. See Table 68.3 for an example case that can be used for case-based small group learning.

Table 68.3 Example case for small group learning

Case presentation	
History of presenting illness	A 67-year-old male with a history of hypertension, hyperlipidemia, coronary artery disease, and prostate cancer (last chemotherapy was 6 month ago) presents to the ED with back pain that began 6 days ago. Reportedly his pain extends from his mid- to lower back, is described as aching and sharp with occasional radiation into his legs bilaterally, and associated with intermittent tingling in his right foot. He says he thinks he may have injured himself while walking his dog but denies fall or specific injury. Additionally, he endorses back pain a few years ago but is unsure if his pain today feels similar. Patient denies fever, chills, bowel or bladder dysfunction, saddle anesthesia, weakness, numbness, history of intravenous drug abuse, or other symptoms
Medical history	Hypertension, hyperlipidemia, coronary artery disease, prostate cancer
Surgical history	Denies
Social history	Drinks alcohol socially, denies tobacco and illicit drug use
Physical exam	Vital signs: BP 156/95 HR 87 RR 98% SpO2 98% on RA T 37.0 General: Awake and alert, mildly cachectic male in no acute distress Skin: Clean, dry, intact, no rash Head: Atraumatic, normocephalic Eyes, ears, nose, throat: Pupils are equal round and reactive to light Neck: Supple, full range of motion, trachea is midline Cardiovascular: Regular rate and rhythm, no murmur, no edema Respiratory: Clear to auscultation bilaterally, non-labored Abdomen: Soft, nontender, nondistended Back: Limited range of motion secondary to pain, tenderness to palpation in the lumbar and thoracic spine Musculoskeletal: Strength is 5/5 to bilateral lower and upper extremities with full range of motion throughout Neurologic: Alert and oriented, sensation is within normal limits, difficulty ambulating secondary to pain without ataxia, deep tendon reflexes 2/4 bilaterally, normal Babinski reflex
Stop: Ask the following questions...	
What is your differential diagnosis?	Malignant spinal cord compression Spinal stenosis Herniated disc Musculoskeletal strain Bone metastasis

Table 68.3 (continued)

What tests would you order for this patient?	Complete blood count Comprehensive metabolic panel Magnetic resonance imaging (MRI) of the cervical, thoracic, and lumbar spine with and without contrast Or computed tomography (CT) scan of the thoracic and lumbar spine (if not at MRI-capable facility)
At this time, provide learners with the lab work and imaging requested for analysis	
What is the diagnosis?	Malignant spinal cord compression
How would you manage this patient?	Administer intravenous dexamethasone 10 mg STAT Consult neurosurgery to evaluate for possible operative intervention Consult radiation-oncologic for emergent radiation therapy Provide pain control Admit to hematology-oncologic or medicine service (if not an operative candidate)
Perform case debrief	
What went well? What did not? Are there any questions pertaining to this case? Has anyone taken care of a patient with malignant spinal cord compression? If so, what were barriers to care? Any general comments or concerns?	
Briefly discuss malignant spinal cord compression	
Include pathophysiology, clinical presentation, diagnosis, and intuition-specific management as well as management pathways based on other clinical scenarios (i.e., at rural ED)	

Simulation, on the other hand, provides more realistic, high-fidelity learning using mannequin simulators or standardized patients. Simulation delivers engaging, team-based active learning that can expose residents to more critical patient scenarios and has been shown to improve comfort in performing procedures, clinical performance, and knowledge retention [12]. Neutropenic fever with sepsis, malignant pericardial effusion with tamponade, spinal cord compression with progressive neurologic deficit, and airway obstruction secondary to a mass are scenarios that are particularly suitable for simulation.

A novel approach to resident education and small group learning known as the "flipped classroom" is also a valuable method for teaching oncologic emergency medicine. With this method, traditional in-class lectures and "homework" are reversed in that learners are assigned content to review at home prior to weekly didactic conference. This homework might include completing an online module, watching a video-recorded lecture, listening to a podcast, or reading a journal article or assigned textbook section to facilitate meeting an educational objective. In conference, instead of a traditional PowerPoint lecture, learners are asked to apply their new knowledge through small group activities requiring them to work through a problem or patient case, with the assistance of a skilled group leader. When successful, this technique creates a framework of core knowledge that is reinforced and cemented through an interactive process [14].

Lastly, longitudinal education in oncologic emergencies throughout the year is helpful to cement knowledge gained through patient encounters and didactic education. This can be done with on-shift bedside teaching, oral board cases, and teaching rounds. Some institutions utilize group sign-out or have a specified time dedicated to a short period of education on a selected topic. This topic could be something selected previously by the scheduled instructor or it could be based on a case encountered during the shift. Additionally, sending a podcast, new journal article, or other nugget of information to residents via email can also enhance their education.

Considering the variable teaching methods outlined above, a curriculum in oncologic emergency medicine that is learner-centered, facilitates engagement, and optimizes knowledge retention can be easily developed. See Table 68.4 for an example of a 10-hour curriculum.

Table 68.4 Example of an oncologic emergency medicine curriculum

Oncologic emergency medicine didactic block		
Day 1		
Subject	Teaching method	Time
Introduction to oncologic emergency medicine	Flipped classroom Pre-conference assignment: Sadik, et al., "attributes of cancer patients admitted to the ED in one year" [3] and/or Rivera, et al., "trends in adult cancer-related emergency department utilization" [6] Alternative method: PowerPoint lecture	30 min
Hematologic derangements and cancer	PowerPoint lecture Including neutropenic fever, blast crisis, hyperviscosity syndrome, leukostasis. Alternative method: Flipped classroom, team-based learning	40 min
Biochemical abnormalities and cancer	PowerPoint lecture Including hypercalcemia, tumor lysis syndrome, hyponatremia (syndrome of inappropriate anti-diuretic hormone), adrenal insufficiency. Alternative method: Flipped classroom, team-based learning	40 min
Break (10 min)		
Immunotherapy and its toxicities	Flipped classroom Identification of immunotherapy agents and CAR-T cell therapies. Toxicities related to these novel agents and potential treatments. Alternative method: PowerPoint lecture, team-based learning	30 min

(continued)

Table 68.4 (continued)

Oncologic emergency medicine didactic block		
Cancer prevention and diagnosis in the ED	PowerPoint lecture and team-based learning Guest from hematology-oncologic to discuss the role of the ED in prevention and diagnosis of management. Alternative method: Flipped classroom	30 min
Neutropenic fever Immunotherapy toxicity Biochemical abnormalities and cancer Difficult communication	Small group: Mix of case-based, team-based learning, and role play Residents will be divided into four small groups, each group will rotate through each small group session. Difficult communication (and breaking bad news) will be done via role play. Alternative method: Simulation, flipped classroom, oral boards, role play	2 hours 30 min at each station
Day 2		
Subject	Teaching method	Time
Topics in palliative care	PowerPoint lecture and group discussion Guest from palliative medicine to review relevant topics including breaking bad news, end-of-life care in the ED, goals of care discussions, etc. Alternative method: Flipped classroom	1 hour
Supportive care in the ED	PowerPoint lecture Outline treatment plans for symptomatic care (i.e., nausea and vomiting). Discuss pain control as it relates to the cancer patient – This may include palliative medicine guest and/or clinical pharmacist. Alternative method: Flipped classroom, team-based learning	30 min
Emergencies related to local tumor effects	Flipped classroom Including superior vena cava syndrome, malignant airway obstruction, spinal cord compression, brain metastasis, malignant pericardial effusion and tamponade, acute airway hemorrhage. Alternative method: PowerPoint lecture, team-based learning, case-based learning	50 min
Break (10 min)		
Chemotherapy, radiation, and associated toxicities	PowerPoint lecture Including extravasation of chemotherapy agents, medication-specific side effects, radiation complications, bone marrow transplant complications. Alternative method: Flipped classroom, team-based learning	30 min

Table 68.4 (continued)

Oncologic emergency medicine didactic block		
Airway obstruction Spinal cord compression Malignant tamponade Topics in palliative care	High-fidelity simulation modules Residents will be divided into four small groups, each group will rotate through the four different simulation sessions. Mannequins for difficult intubation and pericardiocentesis are needed. Alternative method: Case-based learning, team-based learning, oral boards	2 hours 30 min at each station

Implementation

For an oncologic emergency medicine curriculum to be successful, attention must be given to factors important to implementation success. The curriculum developer must ensure that sufficient political and financial support, resources, and administrative structures are in place [4].

First, support should be obtained from curriculum stakeholders. This will include the residency program director and the faculty leader of resident didactic curriculum, followed by the program's core faculty members. Because this curriculum will require preparation and teaching from those responsible for residency education, it is important that core faculty members support the initiative. Additionally, it would likely be beneficial to discuss the curriculum with the hematology-oncologic chair, fellowship program director, or other departmental leaders to ensure that the educational objectives and overall curriculum not only meet the educational needs of the residency, but also properly support the needs of the institution and local cancer population. Furthermore, support should be gained from learners. Adult learners need to understand why learning about oncologic emergencies is important. Having support from learners will foster successful curriculum implementation, particularly when independent learning is required, such as with flipped classroom modules.

Next, adequate resources should be identified. Resources will typically include personnel, facilities, time, and funding (if needed).

Personnel	Curriculum developer/director, expert faculty educators to teach didactics and lead small group activities, simulation director to coordinate simulation sessions, and administrative staff to communicate schedules and collect evaluation reports are all necessary for an oncologic emergency medicine curriculum. If faculty are not experienced with oncologic emergencies, consider faculty development sessions to facilitate enhanced knowledge and skill (see "Continuing Medical Education" further in this chapter).

Facilities	Resident conference room for didactic lectures, small group discussions, and flipped classroom activities. Simulation center for role playing and case-based learning. Clinical site (i.e., ED) to provide an appropriate volume and variable patient presentation to enhance clinical skills. Equipment, including a computer with projector, iPAD for simulation modules, simulation mannequin, software for learning modules, etc.
Time	Curriculum director will need time to coordinate curricular details, analyze evaluations, and provide feedback. Learners require time for independent learning, to attend educational sessions, and to provide feedback. Faculty need time to prepare and teach. Given that oncologic emergencies will be part of an existing resident didactic curriculum, this time is likely already part of core faculty protected hours and professional obligations.
Funding	Depending on the institution, funding may be required to purchase necessary equipment or software to support curriculum implementation. However, intuitions may already have budgets allocating resources for these items or necessary facilities/equipment may already exist and simply need redeployed to accommodate educational activities.

Before beginning a new oncologic emergencies curriculum (or making modifications to an old curriculum), it is advantageous to anticipate and address potential barriers that may occur. Barriers may relate to people, time, education strategies, finances, or other resources [4].

Educators	Competing demands from other job responsibilities or teaching obligations may limit faculty involvement. Limited knowledge of oncologic emergency medicine due to rapidly evolving treatment strategies may require that educators participate in developmental sessions or independent continuing education endeavors.
Learners	Residents may not understand the importance of each educational objective and therefore not actively participate in didactic education. A successful curriculum implementation necessitates comprehensive knowledge retention and achievement of clinical skills and therefore requires that residents take ownership of their own learning by investing time in studying oncologic emergencies outside scheduled conferences.
Time	Providing comprehensive didactic education in only 5 hours a week during residency is a challenging task. Additionally, residents are not always available to attend conference due to variable clinical rotation requirements, duty hour restrictions, or dispersal to different clinical sites.
Education strategies	When using a flipped classroom teaching strategy, if learners do not complete the pre-conference assignment, it limits the likelihood of a successful in-conference session. In addition, quieter residents or those who do not like to speak in groups may not benefit from in-conference discussion [14].
Funding or other resources	There may not be funding to support a curriculum developer/director or to purchase equipment or software that will enhance resident education.

Once support has been gained, resources allocated, and barriers addressed, it is time for curriculum implementation. Typically, this type of curriculum will not need a formal pilot period prior to full implementation. However, it may be worthwhile to pilot simulation and case-based learning sessions with fellow faculty members or residents to ensure they are designed appropriately to achieve educational objectives and knowledge retention. If flaws are discovered, adjustments can be made accordingly. Once piloting is complete, the new or improved oncologic emergency medicine curriculum should be scheduled into the overall resident didactic program.

Following implementation, a plan should exist for curriculum maintenance and enhancement based on feedback and evaluation. A curriculum developer may consider the first year of implementation a "pilot" cycle during which time achievement of goals and objectives is assessed, feedback from residents and faculty obtained and contribution to milestones analyzed. This information can then be used to refine the curriculum for subsequent cycles with a strategy in place for continuous improvement [4].

Evaluation and Feedback

Importantly, consideration should be given to maintaining and enhancing the oncologic emergency medicine curriculum over time. Evaluation helps judge whether goals and objectives were met, provides information that can be used to improve or alter the curriculum, allows for the assessment of resident achievement, and can serve as data for possible publication. Evaluation methods and questions should be developed based on the desired outcome and information sought [4].

The development of feedback should be methodical. First, the curriculum director should identify users of the evaluation, including residents, faculty instructors, program director, and the curriculum developer. Depending on the institution, this may also include the department chair, a hematology-oncologic representative, and individuals or organizations providing financial contributions. Additionally, consider how the evaluation will be used [4]. For the oncologic emergencies curriculum, this will include performance assessment of both the learners (i.e., residents) and the entire program.

Users	Residents will use evaluation and feedback information to understand and improve their own performance and clinical skills. Faculty instructors/small group leaders will use the data to enhance their teaching methods and delivery, thereby improving learner satisfaction. Curriculum developer/director will use the data to discover strengths and weaknesses of the program resulting in improved educational strategies. Program leadership will use resident evaluations and feedback to assist with assessment of achievement of clinical competencies and milestones.

Availability of resources will dictate evaluation questions and methodology [4]. For the purposes of an oncologic emergency medicine curriculum, necessary resources are not extensive, minimizing a potential barrier in obtaining feedback.

Resources	An online platform is needed to serve as a channel for residents and other individuals to complete evaluations. This can be done through residency management software (e.g., New Innovations®, Uniontown, OH). Administrative support staff or the curriculum director is needed to assist with evaluation requests and data analysis.

Evaluation questions should be congruent with curriculum objectives and relate to a specific learner, process, or clinical outcome [4]. During the first year of curriculum implementation, evaluations should be completed at the end of a pre-conference assignment, following a lecture, small group learning exercise, or simulation session, and after the curriculum is complete. This will allow the developer to assess the effectiveness of the curriculum and make necessary changes. In the subsequent years, evaluations can be tailored more toward the instructor, teaching method, and learner.

Resident Evaluation questions	Questions will be answered as strongly agree, agree, neutral, disagree, strongly disagree, and not applicable: The resident appeared to complete pre-conference assignments. The resident was engaged and paid attention to presentations. The resident performed adequate history and physical exam. The resident developed an appropriate differential diagnosis and management plan. The resident demonstrated clinical reasoning skills during case-based learning activities. The resident actively participated in small group activities. The resident communicated effectively with other residents in their group. The resident demonstrated professionalism and respectability toward peers and faculty instructors.
Faculty evaluation questions	Questions will be answered as strongly agree, agree, neutral, disagree, strongly disagree, and not applicable: I was impressed by the faculty member's overall knowledge of oncologic emergencies. The content presented is relative to my education and practice. The presentation was evidence based and without bias. The faculty member was an effective teacher with clear educational objectives. The faculty member communicated effectively with residents during small group education.
Curriculum evaluation questions	What do residents identify as major strengths and weaknesses of the oncologic emergencies curriculum? How could the curriculum be improved? What was the perceived effectiveness of the PowerPoint lectures, small group learning, simulation sessions, pre-conference assignments, and flipped classroom modules in providing valuable education on oncologic emergencies?

Finally, adequate data should be collected to ensure useful analysis. Failure to collect important information or low response rates can compromise the value of an evaluation. Data collection, therefore, should be designed to maximize response rates, practicality, and efficiency of evaluation completion. Following collection, data must be analyzed and reported. When considering how to report assessment information, it is helpful to consider the needs of users. Specifically, residents will benefit from immediate feedback to allow for the information to be processed while the experience is still fresh in their mind [4].

Data collection	Electronic collection of individual and curriculum assessment should be utilized. This can be implemented within an already existing generic evaluation method or a more specific approach can be developed. Each component as well as the overall oncologic emergencies curriculum should be evaluated separately. During the first year of implementation, it is advantageous to obtain specific data on instructional strategies, teaching methods, individual instructors, and overall program content, to maximize curricular enhancement and address unforeseen issues.
Data analysis	Analysis of completed evaluations should occur in real time to optimally facilitate necessary changes while the memory of curriculum details and experience are fresh.
Reporting of results	Immediate formative feedback should be given to residents following any small group activity involving direct observation by a faculty member. If significant concerns are appreciated, this information should be given to the residency program director. Reported feedback should be constructive, using succinct, clear language. A summary of formative and summative information must be given to the curriculum director so that improvements can be made and unmet curricular needs assessed.

While the general process of evaluation and feedback can be cumbersome, it is essential to assess resident learner performance and to guide effective education.

Medical School Education in Oncologic

Acquiring knowledge and clinical skills that will enable physicians to optimally care for cancer-related emergencies begins with undergraduate medical education. Medical

school is essential to provide a foundation of cancer knowledge that can be expanded upon during residency. However, delivering a comprehensive oncologic curriculum to medical students is challenging due to the field's multidisciplinary nature and lack of data on effective teaching approaches [15, 16]. To better characterize oncologic education, surveys of medical students across the United States suggest the following: students are significantly more confident in the basic science of cancer than in workup/diagnosis, treatment, and interacting with oncologists; pre-clinical oncologic education is often fragmented and varies considerably among intuitions [16]; and few schools have mandatory clinical clerkships dedicated to oncologic [15, 16]. Cancer was also found to be under-emphasized in medical school curriculums [15]; it is the second leading cause of death in the United States (behind heart disease) [17], yet it reportedly receives the fourth most curricular time among the six most common causes of death [15].

Another component introduced during medical school and relevant to caring for patients with cancer-related emergencies is palliative and end-of-life care. Palliative care can (and should) include patient and family communication to discuss goals of care, pain and symptom management for critically ill and dying patients, coordination of care, and optimizing quality of life. US medical schools are not currently required by the Liaison Committee on Medical Education (LCME) to teach palliative care, though it does necessitate that curricula include instruction on end-of-life care. The Association of American Medical Colleges (AAMC), however, does recommend that undergraduate medical students learn about shared decision making, communication of bad news, advanced directives, end-of-life wishes, do-not-resuscitate orders, and palliative care [18].

Surveys collected every 5 years since 1975 find dramatic variability among medical schools on the amount of time spent teaching end-of-life care, ranging from 2 to 80 hours over 4 years. Less than one-third reported a clerkship dedicated to end-of-life care, and of these, only one-half are required. All but one responding medical school provided dedicated palliative care education. Another survey reports that of 47 responding medical schools, 30% had a required course, 19% had a required rotation, 15% offered an elective, and 7% offered no course or rotation. The remaining 29% of schools integrated palliative care teaching within another mandatory rotation. Fourth-year students receiving formal training in palliative care reported superior competence and knowledge in caring for the critically ill and dying [18].

This analysis of undergraduate medical education in oncologic and palliative care indicates that medical schools can benefit from a more defined curriculum. With enhanced cancer survivorship, the need for cancer-related knowledge and skills among generalists and specialists will increase proportionally [16]. However, given the limited amount of didactic time available for any one area of medicine, developing an effective oncologic curriculum is challenging. Neeley et al. suggest the following [15]:

1. Improve the organizational structure and coordination of oncologic didactics across all years of medical school to avoid redundancy or accidental omission of content and to ensure there is balance among the types of cancer covered and types of educators who are teaching.
2. Request multidisciplinary contribution to curriculum development to facilitate a more inclusive approach to teaching cancer management.
3. Avoid pure disease-site and organ-system-specific courses; instead supplement them with education on general principles of oncologic, survivorship care, palliative medicine, and the role of primary care physicians in cancer prevention, diagnosis, and management.
4. Create a multidisciplinary oncologic clerkship that provides broad exposure to caring for patients with cancer and incorporates outpatient oncologic exposure for students who plan to pursue non-oncologic fields of medicine.
5. Support the development of national guidelines for medical school education in oncologic, as has been established in Europe, Canada, and Australia.

Another consideration is to create a course to supplement oncologic education similar to the one developed by the European School of Oncologic (ESO). This elective 5-day training program is dedicated to improving medical students' oncologic knowledge and clinical skills. The program includes education in prevention, epidemiology, clinical presentation, diagnosis, and multimodal therapeutic management. It also includes sessions on oncologic emergencies and palliative care [19].

Finally, optimal medical school education in oncologic must include palliative medicine training. According to Horowitz et al. and Head et al., the following must be considered for our undergraduate medical education: 1) palliative care education cannot be limited to electives; it should be integrated into existing courses, such as the practice of clinical medicine, ethics, and pharmacology, as well as in relevant clinical clerkships; 2) basic principal palliative care competency requirements should be established and implemented in all medical schools; and 3) palliative care training should provide developmentally appropriate education for students to achieve these competencies at each stage of schooling [18, 20].

Hematology-Oncologic Fellowship Training

While many cancer patients with concerning symptoms seek treatment at urgent care centers or emergency departments, they may also present to their oncologic clinic or call an oncologic provider after hours. Oncologists also routinely manage these patients after hospital admission. It is thus vital for hematologists and oncologists to be expert in the diagnosis and management of oncologic emergencies.

Though some experience is gained during internal medicine residency, fellows require more advanced and specific knowledge when they begin treating cancer patients early in their fellowship. Currently, hematology-oncologic fellowships in the United States either disperse inpatient clinical duties (including consult and bone marrow transplant services) throughout all 3 years or concentrate them into a more intense first year of fellowship. Didactics and continuity clinics supplement this training. While these experiences provide fellows with gradual hands-on knowledge and understanding of the diagnosis and management of oncologic emergencies, the establishment of a dedicated educational module early in fellowship would enhance learners' confidence in clinical care.

Oncologic emergencies are broad and encompass every system of the human body. For disease-specific emergencies, they can be categorized and taught via systems [21]. Systems categories include metabolic and endocrine (e.g., hypercalcemia, tumor lysis, adrenal), hematologic (e.g., leukostasis, hyperviscosity), neurologic (e.g., vasogenic edema from brain metastases, malignant spinal cord compression, paraneoplastic syndromes such as Lambert-Eaton), cardiovascular (e.g., pericardial effusion, superior vena cava syndrome), and pulmonary (e.g., pleural effusion, airway obstruction, and hemorrhage). The other major type of oncologic emergencies is treatment-related. This subject is particularly important to hematology-oncologic fellows because their exposure from residency didactics and clinical experience is limited. Some examples include immunotherapy-related adverse events, coronary effects from fluoropyrimidines, arrhythmias from ibrutinib, pulmonary toxicity from bleomycin, thrombotic microangiopathy from gemcitabine, and cytokine release syndrome from CAR-T or blinatumomab.

Ideally, a module in oncologic emergencies would include short, case-based didactic sessions at the beginning of fellowship. Cased-based learning has been shown to promote effective learning through increased engagement and authentic clinical practice scenarios [22]. In case-based learning, specific scenarios that resemble realistic patients are created for learners to solve and generate discussion regarding management and treatment plans. This allows fellows to connect theory to a practice situation, thereby integrating basic science and clinical management resulting in active learning and enhanced retention of knowledge [22]. For example, oncologic pharmacists can be incorporated into case-based learning sessions to provide training on specific chemotherapies and medication toxicities to which most fellows likely would not have had extensive exposure. Educational modules on treatment-specific chemotherapy and other pharmaceutical toxicities can then be incorporated into lectures and clinical discussions spread throughout the year. The goal of these sessions would be to reinforce concepts and management strategies to broaden clinical knowledge and skills throughout fellowship.

Including such a module would be a relatively small change that can be made to most hematology-oncologic fellowships without sacrificing the overall curriculum or other valuable learning concepts. Then, instead of progressive learning over several years, fellows will achieve a better knowledge base earlier in fellowship resulting in enhanced quality of care for cancer patients with emergent conditions. To facilitate widespread implementation of this module, the American Society of Hematology (ASH) and American Society of Clinical Oncologic (ASCO) may be able to help. The ASH and ASCO work with the ACGME to create and enforce program requirements and milestones; they also provide workshops and various online programs for both program directors and fellows. These societies could create a recommended oncologic emergencies module that would enable individual programs to then implement this didactic program in a way that suits their specific educational needs with regard to clinical environment, time, and staffing requirements.

Feedback is fundamental to this process. Once the introductory oncologic emergencies module is complete, learners should be asked to provide feedback and evaluate the teaching methods and educational concepts, and instructors to promote effective change. This should be repeated at the halfway point and the end of the first year of fellowship to gather additional comments or critiques as fellows gain further knowledge and clinical experience. Participation should be confidential so opinions can be voiced freely. Improvements and changes can then be made for the new fellows and the entire educational process can be continually refined.

Oncologic Emergency Medicine Fellowships

As the cancer population grows, more and more will seek emergent care. Understanding this need, two oncologic emergency medicine fellowships have been developed, one at The University of Texas MD Anderson Cancer Center and another at The Ohio State University [23].

The University of Texas MD Anderson Cancer Center opened an academic ED within its comprehensive cancer center in 2010. This 40-bed center provides care to almost 26,000 patients with cancer-related conditions annually (approximately 70 patients per day). Their oncologic emergency medicine fellowship was then established in 2011 to provide additional training in the diagnosis, treatment, and multidisciplinary management of ED cancer patients [24]. This fellowship is 1 year (with an optional second year) dedicated to expanding the knowledge of those interested in pain and symptom management, palliative care, and oncologic emergencies. Each fellow works three 10-hour shifts per week in the ED under faculty supervision, completes in-office research and administrative work 2 days per week, attends weekly didactic presentations for 2 hours, and attends faculty meetings and/or graduate medical education curricular lectures on a weekly basis. Second-year fellows pursue their selected clinical track and a research project. Fellow performance is assessed by the program director through biannual evaluations and faculty observation. Additionally, program feedback is obtained through biannual evaluation of the curriculum [23].

The James Cancer Hospital at The Ohio State University Wexner Medical Center opened its own oncologic ED in 2014. This 15-bed department sees approximately 13,000 patients with cancer each year and functions as an integrated component of their general ED. Their 1-year oncologic emergency medicine fellowship was established in 2017. Each fellow completes 7 months of training in the James ED and 1 month of education with each of the following services: oncologic, hematology, neuro-oncologic, and palliative medicine. Fellows also receive 1 month of protected time to conduct research and work on other scholarly projects. Additionally, each fellow can create their own niche and explore individual interests by pursuing an administration, research, or education path within the fellowship [23].

Continuing Medical Education

Beyond residency and fellowship, practicing physicians must continue to educate themselves in oncologic emergencies. This is important not only to provide quality patient care but also to properly educate learners on this topic at the bedside. Unfortunately, opportunities in continuing medical education specific to cancer-related conditions are limited. Most education focuses on febrile neutropenia, hypercalcemia in malignancy, superior vena cava syndrome, hyperviscosity syndrome, and tumor lysis syndrome, and there is little vetted information on more innovative topics such as immunotherapy toxicities. Nationwide, there are some educational opportunities within professional organizations' yearly conferences, such as the American College of Emergency Physicians (ACEP) Scientific Assembly or Society of Academic Emergency Medicine (SAEM) Annual Meeting. Additionally, there are two conferences dedicated specifically to oncologic emergency medicine: MD Anderson Cancer Center's Oncologic Emergency Medicine conference and Memorial Sloan Kettering Cancer Center's Emergencies in the Cancer Patient course.

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National and Institutional Research Efforts

69

Cielito Reyes-Gibby and Jenny L. Ren

Introduction

Advances in cancer diagnosis and treatment have led to increasing life expectancy of cancer patients. The number of cancer survivors in the United States has more than tripled over the past 30 years to over 16.9 million Americans [1]. As cancer evolves to a chronic disease, and with toxicities arising from cancer treatments including surgery, chemotherapy, radiation, and newer cancer therapies, both disease and symptom management of the cancer patient continue to increase in complexity. Many of these patients receive care in emergency departments as most cancer therapies are provided on an outpatient basis. Rapidly identifying the risk profiles of these patients, along with understanding the timing, sequence, duration, and treatment of disease processes and treatment effects, is the most important challenge faced by practitioners in oncologic emergency medicine.

The National Institutes of Health (NIH) invests about $41.7 billion annually to support medical research in the USA [2]. The majority (80%) of this funding supports extramural research awarded through almost 50,000 competitive grants supporting more than 300,000 researchers from more than 2500 universities, medical schools, and other research institutions in every state. Table 69.1 shows the different NIH institutes and centers and their years of establishment [3]. Each fiscal year, these institutes or centers are required to prepare for the US President and US Congress its best professional judgment on the optimum funding needed to make the most rapid progress in their area of science, including funding research investigators, research training, and education of new investigators. In 1937, the National Cancer Institute became the first institute to be established. No institute is dedicated solely to emergency medicine. Advancing

Table 69.1 Institutes and centers established at the National Institutes of Health (US Department of Health and Human Services)

Institutes and Center	Acronym	Year established
National Cancer Institute	NCI	1937
National Heart, Lung, and Blood Institute	NHLBI	1948
National Institute of Allergy and Infectious Diseases	NIAID	1955
National Institute of Dental and Craniofacial Research	NIDCR	1948
National Institute of Mental Health	NIMH	1949
National Institute of Neurological Disorders and Stroke	NINDS	1950
Eunice Kennedy Shriver national institute of child health and human development	NICHD	1962
National Institute of General Medical Sciences	NIGMS	1962
National eye Institute	NEI	1968
National Institute of Environmental Health Sciences	NIEHS	1966
National Institute on Alcohol Abuse and Alcoholism	NIAAA	1974
National Institute on Aging	NIA	1974
National Institute on Drug Abuse	NIDA	1974
National Institute of Arthritis and Musculoskeletal and Skin Diseases	NIAMS	1986
National Institute of Nursing Research	NINR	1986
National Institute on Deafness and Other Communication Disorders	NIDCD	1988
National Human Genome Research Institute	NHGRI	1989
National Institute of Biomedical Imaging and Bioengineering	NIBIB	2000
National Institute on Minority Health and Health Disparities	NIMHD	2000
Fogarty International Center	FIC	1968
National Center for Advancing Translational Sciences	NCATS	2011
National Center for Complementary and Integrative Health	NCCIH	1998

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the science of oncologic emergencies will require collaboration with scientists from different disciplines, building upon existing research infrastructure and investing on research training for ED practitioners. In this chapter, we review research focusing on oncologic emergencies and present the study limitations identified by the authors, present two ongoing research programs at a national and institutional level, and offer future directions.

Limitations of Published Oncologic Emergency Research

This review discusses common limitations of published oncologic emergency research. We searched PubMed using the following terms: {[Emergency (Title/Abstract) or EM (Title/Abstract) or EMS (Title/Abstract) or ED (Title/Abstract)) and [Cancer (Title/Abstract) or Neoplasia (Title/Abstract) or Oncolog* (Title/Abstract)] and limited to publications within the last 10 years. After review of 444 abstracts, we included 48 articles on cancer patients presenting to the emergency department (Table 69.2) [4–51]. Of note, knowledge gaps in emergency care of cancer patients have already been published in the 2016 "Cancer and Emergency Medicine: Setting the Research Agenda" that identified four main research opportunities and priorities to advance the understanding of oncologic emergency care: (1) collection of epidemiologic data, (2) care of patients with febrile neutropenia, (3) information on acute events such as dyspnea or pain, and (4) palliative care in the ED setting [4]. The topics of most, if not all, included articles in this review touch on one or more of these themes.

Table 69.2 Limitations of published studies on oncologic emergencies

Author-Year	Title	Study type, population	Findings	Limitations
Brown et al. 2016 [4]	The emergency care of patients with cancer: Setting the research agenda	Research agenda	Identified research opportunities and priorities to advance understanding of emergency care: (1) collect epidemiologic data, (2) care of patient with febrile neutropenia, (3) acute events like dyspnea and acute pain, and (4) palliative care in the ED	—
Philip et al. 2018 [5]	The experiences of patients with advanced cancer and caregivers presenting to emergency departments: A qualitative study	Cross-sectional study, 19 patients with advanced CA and ED visit, 10 informal caregivers	ED presentations largely prompted by worsening symptoms or to expedite hospital admission – Many directed to ED by PCP. ED experience: Anxiety, uncertainty with communication, the general environment, symptom management delays. Long waits common. Patients felt relief at receiving care	Limited number of EDs, only two services, English-speaking only
Coyne et al. 2017 [6]	Application of the MASCC and CISNE risk-stratification scores to identify low-risk febrile neutropenic patients in the emergency department	Retrospective cohort study, 230 patients from 2 academic EDs	Presenting with chemo-induced febrile neutropenia, CISNE identified 23% as low risk, highly specific (98.3%) for low-risk cohort for all outcomes (inpatient LOS, upgrade in LOC, clinical deterioration, positive blood cultures, death). Median LOS shorter for low- vs. high-risk patients (3-day difference). MASCC score was much less specific (54.2%) in identifying a low-risk cohort	Misclassification bias (especially for patient symptoms), retrospective study based on chart review, missing data, both sites NIH CA centers, thus increased disease relative to general ED population
Adler et al. 2019 [7]	Validation of the emergency severity index (version 4) for the triage of adult emergency department patients with active Cancer	Analysis of observational cohort, 1008 patients from CONCERN (18 EDs)	ESI scores among ED patients with active CA indicate higher acuity than general ED population. ESI associated with patient disposition/resource use. No significant association between ESI and non-ED based outcomes (hospital LOS, 30-day mortality)	Academic, urban setting. 21% of total ineligible, excluded as too ill or unable to consent, fewer high acuity patients. Resource use not well defined in ESI handbook, underestimated. English-speaking only

Table 69.2 (continued)

Author-Year	Title	Study type, population	Findings	Limitations
Caterino et al. 2019 [8]	Analysis of diagnoses, symptoms, medications, and admissions among patients with cancer presenting to emergency departments	Observational prospective cohort study, 1075 adults with active CA from CONCERN (18 EDs)	Mean age 62 (47% > 64), 51.8% female, 73.9% with CA treatment in preceding 30 days, 62.7% had advanced or metastatic CA. 5 most common ED diagnoses were symptom-related. 7.6% placed in observation, 57.2% admitted. 25% admissions had LOS of 2 days or less. Pain during ED visit present in 62.1%, mean pain score 6.4/10. Pain in 72.2% during prior week. ED opioids given to 59.1% with moderate/severe pain. Outpatient opioids for 47.4% patients (with pre-ED pain), including 57% with quite a bit or very much pain. ED nausea present in 31.3% (47.6 received antiemetics). Antibiotics given to 26.5% (73.3% admitted vs. 54.1% not receiving antibiotics)	Large, urban, academic centers, more CA centers. Community ED differs in patient characteristics, resources, outcomes. May have underestimated severity within participating academic institutions. Didn't enroll all presenting CA patients. Some too ill/couldn't participate. Many non-English-speaking CA patients with limited English report inferior treatment outcomes. Underestimated illness severity, 2 possible effects: (1) symptom severity/frequency, admission rate, hospital LOS, other variables related to severity may represent lower severity, and (2) ceiling effect as more challenging to improve outcomes in healthier group. Couldn't identify use of healthcare services in other hospitals, thus underestimated ED revisit/readmission rates
Mueller et al. 2016 [9]	Frequent emergency department utilizers among children with cancer	Retrospective cohort, PHIS database	Frequent utilizers account for 58% of ED visits. They differed from infrequent users by CA type: 39.3% of frequent users had ALL and 16% had CNS tumors (vs. 21.9%, 24.8%, respectively). Frequent use associated with age 5–9 or 1–4 or age < 1 vs. 15–19. Also Hispanic vs. white, non-Hispanics, urban residence. Few children received no meds, lab, imaging during ED visit	Possible patient undercount as some are diagnosed/treated as outpatients. Only tertiary facilities, possible underestimation of prior care
Richards et al. 2011 [10]	Palliative care symptom assessment for patients with cancer in the emergency department: Validation of the screen for palliative and end-of-life care needs in the emergency department instrument	Prospective observational cohort study, 53 patients	53% subjects male, age 24–88. Most common CA diagnoses were breast, colon, and lung. The SPEED instrument demonstrates reliability and validity	Patient population in tertiary center ED may not generalize to other EDs. English-speaking patients in tertiary center
Ahn et al. 2018 [11]	Comparison of the MASCC and CISNE scores for identifying low-risk neutropenic fever patients: Analysis of data from three emergency departments of centers in three continents	Retrospective, 571 patients from 3 tertiary CA ED centers in USA, UK, S. Korea	MASCC: 89.1% classified as low risk, CISNE: 10.5%. MASCC had more discriminatory power in detecting low risk. Risk scores should be used in conjunction with clinical judgment to identify patients suitable for outpatient management	Misclassification bias due to retrospective nature. Tertiary centers are less generalizable

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Table 69.2 (continued)

Author-Year	Title	Study type, population	Findings	Limitations
Delgado-Guay et al. 2016 [12]	Characteristics and outcomes of patients with advanced cancer evaluated by a palliative care team at an emergency center. A retrospective study	Retrospective case control, 400 patients	Median age 56 years old, 56% female, 61% white, no demographic differences between ED and inpatients. Median time from admission to palliative care 12 h for ED patients vs. 24 h for inpatients. For ED vs. inpatients, symptoms included uncontrolled pain (83%/45%), N/V/constipation (41%/19%), dyspnea (29%/19%). At follow-up, improvement in pain, sleep, Well-being, fatigue, anxiety, appetite, dyspnea, nausea, depression, drowsiness. After PC consults, discharge/admission destinations for ED patients were home (33%), home hospice (7%), inpatient hospice (4%), regional hospital floor (33%), and PC unit (23%). Median duration of hospitalization 92 h for hospitalized ED patients and 125 h for inpatients. Referral to PC from ED led to earlier delivery of PC with earlier control of symptoms. ED patients receiving PC consults had shorter hospitalizations than those receiving PC referral as inpatients	Retrospective – Impossible to estimate causality between PC service involvement in ED patients and outcomes. Highly specialized CA center, unique patients. Difficult to describe all interventions provided by PC to ED patients vs. inpatients. Need multicenter prospective studies at national/international levels
Banala et al. 2017 [13]	Discharge or admit? Emergency department management of incidental pulmonary embolism in patients with cancer: a retrospective study	Retrospective cohort, 193 patients	Selected ED CA patients with incidental PE can be treated safely with low-molecular-weight heparin and discharged. Of 193 patients, 70% discharged, 30% admitted. 30-day survival rate: 99% for discharged, 76% for admitted. 98% received ED anticoagulant (90% LMWH). Incident saddle PEs had higher 30-day mortality. Age, comorbidity, race, CA stage, tachycardia, hypoxemia, and incidental PE location associated with hospital admission	Single center, limited numbers. Retrospective. No randomization of treatment. Health outcomes related to PE not well distinguished from those related to advanced CA. Need larger RCT
Batalini et al. 2017 [14]	Cancer complaints: The profile of patients from the emergency department of a Brazilian oncologic teaching hospital	Cross-sectional, 277 ED visits	Pain was most common complaint (40% visits) > constitutional symptoms (17%) > GI complaints (11%). Abdominal pain most noted pain type (18.4%) with highest rate of recurrence > back pain. Cervical CA (14.8%), breast (11.6%), lung (7.6%). Majority of patients visited ED less than once a month	Single site. No staging data. Patients may visit ED for more than 1 complaint and symptoms overlap. No longitudinal follow-up. Importance of research to finding new therapies
Baugh et al. 2016 [15]	Emergency department management of patients with febrile neutropenia: Guideline concordant or overly aggressive?	Retrospective cohort, 173 ED visits to Dana-Farber Cancer Institute	25% of visits low risk, 75% high risk. Management overall was guideline concordant in 70%, discordant in 98% low-risk patients vs. 7% high-risk patients. Of 52 guideline-discordant cases, 83% involved low-risk cases with more aggressive treatment than recommended	Single-center study. Retrospective chart review. Model may lack important unmeasured covariates. Nonadherence could be due to awareness gap or factors not captured in chart review. Couldn't tell if management plan driven by ED or oncologist. Did not power the study to detect differences in clinical outcomes between risk groups

Table 69.2 (continued)

Author-Year	Title	Study type, population	Findings	Limitations
Brown et al. 2017 [16]	An exploration of medical emergency team (MET) intervention at the end of life for people with advanced cancer	Case control, 100 patients	Cohort without MET intervention had better quality of death score vs. MET patients. Within MET cohort, if MET influenced EOL decision-making (n = 19), had a significantly higher quality of death score vs. MET patients where MET did not influence care	Retrospective chart review. Misinterpretation of quality of death indicators. Single CA center. No record of EOL discussions, family members'/friends' perceptions of quality of death. Need prospective observational study to enhance understanding of MET in EOL CA care
Elsayem et al. 2017 [17]	Advance directives, hospitalization, and survival among advanced cancer patients with delirium presenting to the emergency department: a prospective study	Prospective cross-sectional observational study, 243 randomly selected CA patients from MD Anderson ED	Group A = delirium diagnosed by both CAM and MDAS; group B = MDAS only; group C = neither. Hospitalization rates for A 82%, B 77%, C 49%. ICU rates: 18%, 14%, 2%. Advance directives: 52%, 27%, 43%. Median overall survival: 1.23 month, 4.7 months, 10.45 months. Overall survival did not differ between groups A and B, but group C survival exceeded other groups. Delirium assessed by either CAM or MDAS was associated with worse survival and more hospitalization in patients with advanced CA. Many advanced ED CA patients with delirium lack advance directives	Single-center study. Number of patients small. Did not adjust for comorbidities or illness severity. Did not follow patients longitudinally to evaluate whether further interventions were done during hospitalization or if patients discharged to hospice
Elsayem et al. 2016 [18]	Delirium frequency among advanced cancer patients presenting to an emergency department: A prospective, randomized, observational study	RCT, 243 English-speaking patients with advanced CA from MD Anderson ED	Median age 62. 9% had CAM+ delirium, median MDAS score 14. Patients with delirium had poorer performance status than patients without (but 2 groups did not differ in other characteristics). 10% of age > 64 patients had CAM+ delirium vs. 8% age < 65. Mild delirium in 82%, moderate in 18%. Physicians identified delirium in 59% of CAM+ patients	Single center, small sample. Unblinded ED physicians to potential of delirium in their patients, thus bias favoring more frequent recognition. Selection bias: Excluded unstable patients, refusal, dementia. Could have higher delirium prevalence than those consenting, thus underestimates prevalence of delirium. Did not enroll patients at night
Elsayem et al. 2016 [19]	Presenting symptoms in the emergency department as predictors of intensive care unit admissions and hospital mortality in a comprehensive cancer center	Retrospective cohort, 9246 patients, 16,038 visits to MD Anderson ED	Main presenting symptoms: Pain, fever, dyspnea. 58% admitted to hospital at least once (range 1–13), 13% admitted to ICU at least once, 11% died during hospitalization. Independent predictors of hospital death: Presenting symptoms of respiratory distress or altered mental status, lung CA, leukemia, lymphoma, nonwhite race. Patients who died had longer LOS than those discharged alive	Retrospective, single center. No data on whether patients had advanced progressive or limited disease or whether they were treated for cure or palliation. No tumor staging. Used only main presenting symptoms, many patients had multiple or secondary symptoms. Systematic symptom assessment will allow better understanding of multiple symptoms and their impact on QOL
Kyeremanteng et al. 2019 [20]	Outcomes and cost of patients with terminal cancer admitted to acute care in the final 2 weeks of life: a retrospective chart review	Retrospective cohort, 130 patients who visited ED within 2 weeks of death, the Ottawa Hospital	85% had metastatic disease. 71% of admitted patients did not have advanced care directives. 18% receiving palliative care. Patients hospitalized for 7 days on average. Hospitalization costs 2.5 times estimated hospice cost	Retrospective, single-center study, small sample size. Chart review – Not all data recorded. Cost calculations based on crude estimates

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Table 69.2 (continued)

Author-Year	Title	Study type, population	Findings	Limitations
El Majzoub et al. 2019 [21]	Adverse effects of immune checkpoint therapy in cancer patients visiting the emergency department of a comprehensive cancer center	Retrospective review, 257 ED patients receiving immune checkpoint therapy from MD Anderson ED	25% of visits related to immune-related adverse effects. Diarrhea was most common reason for visit. Proportions of visits associated with diarrhea, hypophysitis, thyroiditis, pancreatitis, or hepatitis varied significantly by immune checkpoint therapy agent. Colitis associated with better prognosis; pneumonitis with worse survival	Single institution, limited size. Physicians performing data abstraction not blinded to outcomes or previous abstraction results when performing data confirmation. EMR may be erroneous. Underestimated true survival (used last confirmed contact when death unverified). Immunotherapy always changing (available agents, approved indications, patient characteristics)
Mueller et al. 2019 [22]	Identifying patient-centered outcomes for children with cancer and their caregivers when they seek care in the emergency department	Cohort, 26 caregivers or children with CA from IU Riley Hospital for children Heme-Onc clinic	More important outcomes included system-level issues (e.g., cleanliness, timeliness) and oncologic-provider or ED-provider level issues (ability to access port-a-caths, quality of communication). Also identified outcomes that were within control of patient/caregiver, such as improving their sense of preparedness	Need future research on development and validation of patient-centered outcomes tool. Single institution – Data may not be representative. Small sample size
Peyrony et al. 2020 [23]	Antibiotic prescribing and outcomes in cancer patients with febrile neutropenia in the emergency department	Cohort, 249 patients	Median age 60, 67.9% hematological malignancy, 10.4% admitted to ICU, 9.8% died during hospital stay. 32.4% of low-risk patients presented at least 1 complication, including 11 deaths. Time to antibiotic initiation in ED not associated with outcome after adjusting for performance status and shock index. Inadequate ED antibiotic regimen associated with higher ICU admission and death during hospital stay (OR = 3.5). An inadequate ED antibiotic regimen in patients with FN was significantly associated with higher ICU admission or death during hospital stay	Retrospective, interpretation bias during chart abstraction. Antibiotic appropriateness may vary between centers. Possible missed confounders. Single-center – External validation needed
Reyes-Gibby et al. 2017 [24]	Cohort study of oncologic emergencies in patients with head and neck cancer	Prospective cohort, 298 patients	History of HTN, normal or underweight BMI, and probably depression predicted increased risk for ED presentation. BMI and severe pain associated with higher frequency of ED presentations	Small sample size. HPV status missing. Limited to patients with HNSCC from 1 tertiary care CA center. Possibly did not capture all ED visits (e.g., other hospital ED). Lack of data on etiology of pain
Reyes-Gibby et al. 2016 [25]	Risk for opioid misuse among emergency department cancer patients	Cross-sectional, 209 patients	On basis of SOAPP-R (screener and opioid assessment for patients with pain-revised) cutoff of 18, 34% patients had high risk of misuse. 15% and 4% of all patients reported past or current use of illicit substances, respectively. Total number of annual opioid prescriptions differed between high- and low-risk groups. Depression, poor coping, and illicit substance use were associated with high risk of opioid misuse	Single center. Patients already receiving opioids – May have affected survey responses. Patient self-report. Number of opioid prescriptions is imperfect representation of actual dosage/pill count. Future studies of patients with CA-related pain should include multiple measures of risk (risky medication-related behaviors, structured interview). Potentially inaccurate alcohol and smoking status. Nonrespondents had higher pain scores

Table 69.2 (continued)

Author-Year	Title	Study type, population	Findings	Limitations
Tanriverdi et al. 2014 [26]	Single center experience on causes of cancer patients visiting the emergency department in Southwest Turkey	Retrospective cohort, 102 patients, 304 ED visits	65% patients male, 52% over age 65. 30% lung CA, 32% with dyspnea, 53% with metastasis, 30% with multiple metastatic lung lesions, 68% had poor ECOG performance status	Small sample size, single center
Yang et al. 2016 [27]	Cardiac troponin is a predictor of septic shock mortality in cancer patients in an emergency department: a retrospective cohort study	Retrospective cohort, 375 ED CA patients with septic shock	Creatine kinase myocardial band fraction and troponin-I significantly higher in patients who died in ≤7 days and ≤28 days than in those who did not. The SOPED (septic oncologic patients in emergency department) scoring system, which incorporated troponin-I, was more prognostically accurate than were other scores for 7-day mortality	Single center, small sample size, retrospective. Results should be verified in large well-designed multicenter clinical study. Advances in management of sepsis occurred during study time. Prognosis of CA patients with septic shock probably not generalizable to non-CA
Lamb et al. 2019 [28]	Hodgkin lymphoma detection and survival: Findings from the Haematological malignancy research network	Cohort, 971 patients	Median diagnosis at age 41.5, 55.2% male, 31.2% stage IV. 43% had moderate to high or high-risk prognostic score. 18.7% admitted via ED prior to diagnosis. Relationship between age and ED admission was U-shaped: More likely in patients <25 and > = 70. Compared to patients admitted via other routes, those via ED had more advanced disease and poorer survival. After adjusting for clinically important prognostic factors, no difference in survival remained	Lack of primary data, could not investigate patterns or referrals from primary care, Hodgkin lymphoma is rare
Mayer et al. 2011 [29]	Why do patients with cancer visit emergency departments? Results of a 2008 population study in North Carolina	Observational, 2008 NC DETECT ED visit data, 37,760 ED visits, 27,644 CA patients	77.2% of patients had 1 ED visit in 2008. Mean age 64, slightly more men. Among visits, Medicare 52.4%, Medicaid 12.1%. >1/2 visits weekends or evenings, 44.9% during office hours. Top 3 complaints: Pain, dyspnea, GI issues. Lung, breast, prostate, and colorectal CAs had largest proportions. 63.2% visits resulted in hospital admission. Patients with lung CA were more likely to be admitted than other CA types	All data collected for other purposes. No associations between county of residence, site of usual healthcare, and location of ED (NC DETECT didn't allow identifying information). No data on whether patients were under clinical care or where. No race/ethnicity data. Some visits that were CA-related may have been missed, some visits that were not CA-related may have been included. Not possible to identify visits by patient to multiple EDs. Limitation to categorization of presenting symptoms (not exhaustive/completely inclusive). Not possible to tell if some patients visited local EDs because routine care was at a CA center far from home. If healthcare services had been available, could those patients have avoided an ED visit? Need more info about these patients before and after their visits

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Table 69.2 (continued)

Author-Year	Title	Study type, population	Findings	Limitations
Mueller et al. 2016 [30]	Characteristics of children with cancer discharged or admitted from the emergency department	Retrospective, 26,770 ED visits, 17,943 children with CA from 39 children's hospitals	Half of children with CA visited ED within 1 year after their first CA hospitalization in pediatric health information system (PHIS). 56% of ED visits resulted in admission. Fever and neutropenia were most common reasons for visits (34.6%). Risk factors: "Other" race/ethnicity, history of transplant, and ED visits reasons including neutropenia, bloodstream infection, pancytopenia, dehydration, or pneumonia	Some patients diagnosed and treated as outpatients. PHIS does not include data on disease status, treatment, or time since last treatment for patient when they visit ED. discharge ICD-9 codes limits understanding of chief complaints to ED, thus lacks key data for anticipatory guidance. Extrapolated reasons for ED visit from ICD codes rather than the initial complaint. Only single diagnosis evaluated per patient encounter, but children with CA may present to ED with multiple problems
Mueller et al. 2020 [31]	Variation in hospital admission from the emergency department for children with cancer: a pediatric health information system study	Retrospective cohort, 60,054 ED visits for children with CA, using PHIS data	62.5% admitted, primary diagnosis – Fever. Largest variability in admission rates. Less variability among hospital admission rates for neutropenia and febrile neutropenia. Admission rates by day of the week did not demonstrate significant variability and no differences seen between weekend and weekday	ICD codes may not accurately identify all CA patients, leading to over/underestimate of ED cases. PHIS data set did not reliably detect ED chief complaint – Extrapolated from ICD9 codes. Variability in coding by hospital, PHIS did not include all hospitals that treat children with CA. No access to important clinical data. Did not account for holidays
Patel et al. 2017 [32]	Evaluation of emergency department management of opioid-tolerant cancer patients with acute pain	Retrospective cohort study, 216 patients Opioid-tolerant CA patients who received opioids in ED over 2 years	61.1% of ED patients received adequate initial PRN dose of opioids. Of patients taking <200 OMEs per day at home, 77.4% received an adequate initial dose. 3.2% of patients taking >400 OMEs per day at home received an adequate dose. Patients with ambulatory 24-hour OME greater than 400 had 99% lower odds of receiving an adequate initial dose of PRN opioid in the ED compared to patients with ambulatory 24-hour OME less than 100	Retrospective study. Assumed patients were taking meds as prescribed. May have been skewed to higher ambulatory use. Not all ED visits studied were primarily for pain-related complaints. Didn't assess whether CA was active/ inactive during study period. Not enough patients at extremes of age pain scores not routinely documented
Sadik et al. 2014 [33]	Attributes of cancer patients admitted to the emergency department in one year	Retrospective review, 408 ED CA patients	58.8% male, median age 57.9, 65.3% had metastatic disease. Hospitalization rate 59.6%. Most common symptoms were dyspnea, pain, fever, and N/V. Most common CA sites were lung, GI, and breast. Initial evaluation found progressive disease, chemotherapy effects, infections, radiotherapy effects, extravasation, anemia, and unknown. During follow-up, 46.8% patients died after admission to ED. 1-year overall survival of all patients was 7.3 months	Retrospective. Survival data collected from diverse sources, including telephone surveys

Table 69.2 (continued)

Author-Year	Title	Study type, population	Findings	Limitations
Seow et al. 2016 [34]	Does increasing home care nursing reduce emergency department visits at the end of life? A population-based cohort study of cancer decedents	Retrospective cohort, 54,576 EOL cancer decedents in Ontario, Canada	Of decedents using home care nursing services in last 6 months before death, 85% had ED visit, and 68% received EOL home care nursing. Patients receiving EOL nursing vs. standard nursing had reduced ED rate. In last month of life, receiving EOL nursing and standard nursing rate of >5 hours/week was associated with fewer ED visit rates of 41%. Temporal association between receiving end-of-life nursing in a given week during the last 6 months of life and of more standard nursing in the last month of life was associated with a reduced ED rate in the subsequent week	Retrospective – No causality. Administrative databases limited – No data on caregiver support, patient clinical/psychosocial, physician care, symptom severity, or privately obtained home care services. Does not analyze reasons for ED visits. Canadian system
Scholer et al. 2017 [35]	Improving cancer patient emergency room utilization: A New Jersey state assessment	Retrospective cohort, 37,080 ED CA visits in New Jersey	Most frequent diagnosis: Lung CA (30%), most common complaint: Pain. Patients who visited ED predicted by race, age 65–75, number of diagnosis, insurance payer, CA type. Comorbidities increase mortality, being transferred to SNF/ICF, using home healthcare services. Readmission is affected by race, income, and type of CA	No causality. Secondary data collected for other purposes. No hospital/ED facility ID information or revisits. Need ability to link healthcare data from SEER, Medicare, Medicaid, to allow a more comprehensive view on participating events, sequelae after ED visit, and effect of multimodal treatment
Qdaisat et al. 2020 [36]	Evaluation of cancer patients with suspected pulmonary embolism: Performance of the American College of Physicians Guideline	Retrospective, 380 patients	56% received CT pulmonary angiogram (CTPA) per ACP guideline, 21% received CTPA not per guideline. Pulmonary embolisms (PEs) were in 6% low-risk, 10% intermediate-risk, and 25% high-risk patients. ACP guideline had NPV of 99% and sensitivity of 97% in predicting PE	Retrospective. Inclusion of only patients who underwent CTPA
Grudzen et al. 2016 [37]	Emergency department-initiated palliative care in advanced cancer: a randomized clinical trial	RCT, 136 patients	QOL higher in palliative care group. Median estimates of survival were longer in PC group, but not significantly. No statistically significant differences in depression, admission to ICU, or discharge to hospice	Variable length of survival in cohort. Need future trial that limits enrollment to patients at similar CA stage. Unable to ascertain whether ICU admit/hospice referral was a reflection of patient's goals of care or if reflection of what team offered the patient. Missing data – Many patients did not survive for follow-up

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Table 69.2 (continued)

Author-Year	Title	Study type, population	Findings	Limitations
Vandyk et al. 2012 [38]	Emergency department visits for symptoms experienced by oncologic patients: a systematic review	Systematic review, 18 studies cited in Medline, Embase, PsycINFO, and CINAHL	Of 28 symptoms reported, most common were febrile neutropenia, infection, pain, fever, and dyspnea. Definitions provided for individual symptoms were inconsistent. ED visits resulted in hospital admissions 58% (median) of the time in multi-symptom studies and 100% of the time in targeted symptoms studies. 13% (median) of ED visits captured in multi-symptom studies (range 1% to 56%) and 20% (median) of visits in targeted symptoms studies (range 4% to 67%) resulted in death	Few symptoms were defined adequately to compare data across studies (gap in CA symptom reporting). Symptom definitions inconsistent or not provided. Combined prevalence of any symptom could over−/under-represent actual ED use. Need better use of standardized definitions to improve reliability/validity of reporting/facilitate synthesis across studies. Need research exploring the impact of risk of exposure to communicable disease on health of oncologic patients visiting EDs. Sample sizes varied significantly. Sometimes repeat visits by single patients were excluded possible that patients who needed ED care most were under-represented. Mortality inconsistently reported (rates collected at different intervals). In most articles, unclear whether authors identified confounding factors or if analyses took them into account
Baugh et al. 2019 [39]	Near-universal hospitalization of US emergency department patients with cancer and febrile neutropenia	Observational, 348,868 ED visits	94% of ED visits resulted in hospitalization. Private, self-pay, and other insurance were less likely to be hospitalized than those with public insurance. Hospitalization was least likely at non-metropolitan hospitals and metropolitan non-teaching hospitals. 26% of variability in hospitalization rate was attributable to which hospital the patient visited	Case ascertainment depended on diagnostic codes, which may be subject to error. Codes used to specify neutropenia did not specify a definition. Lack of a single discharge code describing FN may have also led to an underestimate of the true number of cases. NEDS does not track revisits by the same patient
Huang et al. 2020 [40]	Review article: End-of-life care for older people in the emergency department: A scoping review	Review, 14 articles	Definitions pertaining to EOL care in the ED vary. Older people presenting to ED at EOL were mostly female, triaged in urgent or semi-urgent category, presented with diagnoses of advanced CA, cardiac and pulmonary disease, and dementia with symptoms including pain and breathlessness. Multiple tools pertaining to EOL exist and range from predicting mortality and assessing functional status, comorbidities, symptom distress, palliative care needs, quality of life, and caregiver's stress. Outcomes for older people enrolled in specific EOL intervention programs included lower admission rates, shorter ED length of stay, increased palliative care referral and consultations, and decreased Medicare costs	Limited evidence exists regarding the definition, clinical profile, care delivery and outcomes for older people requiring EOL care in the ED

Table 69.2 (continued)

Author-Year	Title	Study type, population	Findings	Limitations
Lee et al. 2015 [41]	Emergency visits among end-of-life cancer patients in Taiwan: a nationwide population-based study	Retrospective cohort, 32,772 ED CA patients in Taiwan	81.5% ED visits in mortality group; higher ED utilization significantly monthly to EOL. Most frequent CA types were digestive and peritoneum CA (35%), breast (17.7%), and H&N (13.3%). Older patients, males, metastatic disease, and respiratory or digestive CA were more likely to use ED services at EOL. Use of an ED service in nearest community hospital to replace centers for dying CA patients would be more acceptable in emergency situation	If patient suffered prolonged hospitalization in last 6 months of life, may underestimate ED utilization. Loss of detail in claims data mining. Possible confounders not controlled, including socioeconomic status and family support
Mills et al. 2019 [42]	Factors affecting use of unscheduled care for people with advanced cancer: a retrospective cohort study in Scotland	Retrospective cohort, 2443 CA deaths in Tayside, Scotland	Of those dying from CA, 77.9% attended unscheduled care in the year before death. Among these, 10.7% A&E only and 33.1% both (along with GP). 19.7% attendances in last week, 36.7% last 4 weeks, 60.3% last 12 weeks of life. Age, sex, deprivation, and CA type not associated with unscheduled care attendance. Rural areas less likely to attend unscheduled care. Pain was most frequent coded clinical reason for presenting. Of those dying from CA, 21% were frequent users (> = 5 attendances/year) and account for over half of unscheduled care attendances	Variable clinical coding of reason for attendance. Non-specific/ missing coding
Panattoni et al. 2018 [43]	Characterizing potentially preventable cancer- and chronic disease-related emergency department use in the year after treatment initiation: a regional study	Cohort, 5853 eligible patients, 2400 visits within 1 year of treatment	27% had at least 1 ED visit. 49.8% of ED visits had a potentially preventable diagnosis. The prevalence of potentially preventable ED visits was generally high, but varied depending on the diagnosis code fields and the group of codes considered	Claims records are imperfect proxies in CA. Validation studies needed to determine best uses and methodological approach to measuring potentially preventable ED use. Commercially insured population – can't extrapolate to Medicare, Medicaid, or other regional groups. Excluded ED visits with a direct transfer to inpatient hospitalization, likely undercounts all potentially preventable adverse outcomes. Other issues beyond symptoms may influence ED use – Fear, cultural background, insufficient language/ communication skills, delays in seeking help, nonadherence, and lack of social support

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Table 69.2 (continued)

Author-Year	Title	Study type, population	Findings	Limitations
Rivera et al. 2017 [44]	Trends in adult cancer-related emergency department utilization: An analysis of data from the nationwide emergency department sample	Observational, 7 survey cycles from Nationwide emergency department sample (NEDS), 29.5 million CA patients, 696 million adult ED visits	Of all adult ED visits, 4.2% were by patients with CA. Most common were breast, prostate, and lung CA. Most common primary reasons for visit were pneumonia, nonspecific chest pain, and urinary tract infection. Adult CA-related ED visits resulted in inpatient admissions more than non-CA-related visits. Septicemia and intestinal obstruction were associated with highest odds of inpatient admits	Inherent limitations of data set. If a patient with CA visited ED and CA code not documented, then patient was misclassified into nonCA visit group. No separate CA staging/ treatment codes in NEDS data set other than maintenance chemo or radiotherapy, thus not possible to distinguish type of treatment or whether patients were receiving active treatment, already completed, or advanced disease. Lack of detailed staging and treatment data – Unable to examine reasons for CA-related visits at points along CA continuum. Primary reason for visit based on codes – Not enough detail. Need more detailed data on reason for visits to ED and those related to patient's CA (date of diagnosis, CA type/stage, previous treatment, and clinical outcomes)
Tang et al. 2017 [45]	An analysis of emergency department visits and the survival rate for colorectal cancer (CRC) patients: a nationwide population-based study	Retrospective cohort, 6532 ED visits by 3347 colorectal patients in Taiwan	Top three most common reasons ED visits: Ill-defined conditions, abdominal pain, and intestinal obstruction. Overall survival rates of colorectal patients in the ED visit group at 3, 5, and 10 years were 0.65, 0.56, and 0.47, respectively, without significant differences from rates among colorectal CA patients who did not visit the ED	Did not differentiate end-stage patients from general patients with CRC. Unable to detect actual reason for ED visit. ICD system designed for general purposes, not fit to describe CA-associated problems
Liao et al. 2017 [46]	Effects of multidisciplinary team on emergency care for colorectal cancer patients: A nationwide-matched cohort study	Observational study, 45,418 patients with newly CRC diagnosis, Taiwan National Health Insurance Research Database	Odds ratio (OR) by probability of emergency care used for participation in multidisciplinary care groups (MDT) within a year of CA diagnosis was less than that for nonparticipation. Significant benefits of MDT in CRC care	Secondary database. Patient ED care by urgency level not addressed
Yap et al. 2018 [47]	Patterns of care and emergency presentations for people with non-small cell lung cancer in New South Wales, Australia: A population-based study	Retrospective cohort, 647 NSCLC cases in Australia	58.6% male, median age 73. ED presenters (34.5% of cases) were more likely to have a high Charlson comorbidity index score, be an ex-smoker who had quit in the past 15 years, and be diagnosed with distant metastases. Almost all patients had visited their general practitioner ≥3 times in the 6 months prior to diagnosis. Nearly one-third (29.5%) of patients did not receive any anti-CA treatment; however, there were no differences between emergency and non-emergency presenters in the likelihood of receiving treatment. Those less likely to be treated were older, had no private health insurance, and had unknown stage disease recorded	45 and older sample, not whole NSW population. Could not directly infer that patients who visited ED in month/month prior to diagnosis were detected as a result of ED presentation. No access to more detailed TNM staging or ECOG performance status. 19% unknown stage

Table 69.2 (continued)

Author-Year	Title	Study type, population	Findings	Limitations
Hryniewicki et al. 2018 [48]	Management of immune checkpoint inhibitor toxicities: a review and clinical guideline for emergency physicians	Review, 50 articles via PubMed	Inhibition of immune checkpoints may lead to loss of peripheral tolerance and subsequent unleashing of immune system on nontumor cells, leading to unintended tissue damage and multisystem organ dysfunction. Most commonly affected organ systems are dermatologic, GI, endocrine, and pulmonary. Treatment can range drastically depending on severity of irAE (immune-related adverse events): Supportive care, high-dose steroids, additional immune modulators (infliximab, IVIG)	Further studies needed to analyze outcomes of different treatment strategies in patients presenting with potential immune-related adverse events
Knight et al. 2017 [49]	Acute oncologic care: A narrative review of the acute management of neutropenic sepsis and immune-related toxicities of checkpoint inhibitors	Review	Outpatient management of low-risk febrile neutropenia patients identified by the MASCC score is a safe and effective strategy. Immunotherapy with "checkpoint inhibitors" has significantly improved outcomes for patients with metastatic melanoma, and evidence of benefit in a wide range of malignancies is developing. Timing of the onset of the adverse events is dependent on the organ system affected and unlike anti-neoplastic therapy can be delayed significantly after initiation or completion of therapy	Further research into optimal management, strategies, and pathways of acutely ill CA patients is required
Bowers et al. 2017 [50]	Ketamine as an adjunct to opioids for acute pain in the emergency department: a randomized controlled trial	RCT, 116 patients	Patients receiving ketamine reported lower pain scores over 120 minutes than patients receiving placebo. Total opioid dose was lower in the ketamine group. Satisfaction did not differ between groups. Fewer patients in the ketamine group required additional opioid doses. More patients reported light-headedness and dizziness in the ketamine group	Cohort with chronic pain and long-term outpatient opioid use may react differently to the adjunctive ketamine usage than patients with new-onset acute pain. ED environment allows for less precise control of variables. Subjectivity of patient-reported values. Sometimes a time point was missed
Northfield et al. 2019 [51]	Taking care of our own: A narrative review of cancer care services-led models of care providing emergent care to patients with cancer	Review, 22 studies	Overarching outcomes associated with the most commonly described models of care (telephone advice services and/or unplanned care and assessment units) were improved coordination of care/continuity of care, prompt access to specialist care, reduced utilization of EDs, fewer hospital admissions, and reduced cost	Methodological weaknesses of included studies and variations in study designs, settings, and models of care. Future studies should explore patient and caregiver CA experiences

CA cancer, *CAM* Confusion Assessment Method, *CISNE* Clinical Index of Stable Febrile Neutropenia, *ECOG* Eastern Cooperative Oncologic Group, *EOL* end of life, *ESI* emergency severity index, *HNSCC* head and neck squamous cell carcinoma, *HTN* hypertension, *LMWH* low-molecular-weight heparin, *LOS* length of stay, *MASCC* Multinational Association of Supportive Care in Cancer, *MDAS* Memorial Delirium Assessment Scale, *NIH* National Institutes of Health, *OME* oral morphine equivalent, *RCT* randomized control trial, *SEER S*urveillance, Epidemiology, and End Results Program

The most commonly cited limitation of all articles was generalizability. Majority of studies were conducted in an academic, urban setting (community hospital ED cancer prevalence and care may differ) [5–8] at tertiary cancer centers [9–12] or a single center (which may have limited the number of patients in the study) [13–27]. Selection bias was identified for including only English-speaking patients [5, 7, 8, 10]. Furthermore, patients that were too ill or unable to consent were deemed ineligible, which may have underestimated the severity of patients presenting to the ED [7, 8, 18, 25]. As a result, many studies reported the lower bounds of severity and acuity and therefore may contribute to a ceiling effect (when it is more challenging to improve outcomes in a healthier subset) [8].

Most studies were retrospective [6, 9, 11–13, 15, 16, 19–21, 23, 26–36], often relying on chart review, which may lead to misclassification bias when data were misinterpreted or missing [6, 11, 16, 20, 21, 23, 25, 28, 29, 36, 37]. Additionally, many of the studies reported a lack of longitudinal follow-up, complicated by different timing and measures of mortality rates [14, 17, 21, 29, 35]. Some studies claimed they could not track revisits by the same patient, possibly counting some patients more than once, or they were unable to identify visits by the same patient to different EDs [24, 29, 38, 39].

Another common limitation identified by the authors was the inaccuracy and/or inadequacy of diagnostic codes – there was no standardization of definitions of chief complaints, as well as limited categorization [19, 29–31, 38–45]. Therefore, the true number of cancer patients presenting to emergency centers may not be accurately represented [31, 39, 44]. It was also difficult to account for multiple symptoms, as health records and ICD-9 codes often only reported the main presenting symptom used to assess ED admissions [14, 19, 30]. The databases used for many of these retrospective studies were secondary data and thus limited in the types of information recorded [28, 29, 34, 35, 46]. Many articles reported lack of staging information [14, 19, 44, 47] and disease or treatment status [19, 30–32, 37, 44, 45, 47] (e.g., advanced, progressive, or limited disease, new diagnosis or continued care, active or inactive cancer). It was also unclear whether multiple models lacked unmeasured confounders or if the analyses were adjusted for their potential confounding effect [15, 23, 38, 41, 43]. This would include factors such as socioeconomic status, family support, cultural background, delays in seeking help, medical nonadherence, and lack of social support.

Other limitations focused on the evolving field of cancer treatment, which may have altered findings throughout the duration of the study. For example, two articles focusing on immunotherapy discussed the rapidly changing field and newly identified immune-related adverse events [21, 48]. Another two articles pointed out that sepsis management of cancer patients in the ED also changed during the respective studies [27, 49]. Multiple papers also called for novel research on pain in patients with cancer presenting to the ED [14, 24, 25, 32, 50]. These authors pointed out that their population had a mix of chronic and acute pain complaints, and their results may have been confounded by possible opioid tolerance in some patients [25, 50]. In addition, pain scores were not routinely documented [32] and no data had been published on the etiologies of cancer pain [24]. Patient-reported pain scores and satisfaction levels also have an inherently subjective nature [25, 50]. Lastly, some publications identified the gap in knowledge on patients' goals of care and how that may influence their experience in the ED [37, 51].

Overall, there is a need for larger, prospective cohort studies of oncologic patients presenting to the ED that would allow for understanding readmissions/revisits and re-hospitalizations, multicenter randomized control trials, and inclusion of diverse populations. There is also a need for more accurate, standardized recording of diagnoses of patients presenting to the ED, including a systematic assessment of those with multiple symptoms. Given the rapid advances in cancer treatment, developing risk profiles of cancer patients, along with understanding the timing, sequence, and duration of toxicities of cancer treatment, is needed.

Training Opportunities

Given the large amount of existing federal funding in support of cancer research, there are many opportunities for academic emergency physicians to partner with their colleagues in other specialties who study cancer-related emergencies. This is particularly true for academic departments of emergency medicine situated in one of the 41 National Cancer Institute-designated comprehensive cancer centers. These centers offer a number of institutional research training programs (e.g., National Research Service Awards – T32 grants) that can deliver formal research training to junior academic emergency physicians who wish to pursue traditional research careers.

The Comprehensive Oncologic Emergencies Research Network (CONCERN)

In March 2015, the National Cancer Institute and the Office of Emergency Care Research sponsored a 1-day workshop, titled "Cancer and Emergency Medicine: Setting the Research Agenda," in Bethesda, MD. The goal of the workshop was to identify research opportunities and determine research priorities for issues related to the emergency care of

Table 69.3 Partial list of workshop recommendations from the March 25, 2015, workshop titled "Cancer and Emergency Medicine: Setting the Research Agenda," in Bethesda, MD, sponsored by the National Cancer Institute and the Office of Emergency Care Research

Topic[a]	Areas of concern			
Emergency department (ED) use by cancer patients	Definition of a cancer patient	Definition of a cancer-related ED visit	Electronic medical records	Options for ED care
Febrile neutropenia	Definition of febrile neutropenia; objective response	Optimal treatment strategies	Effects of timing of antibiotic therapy	Biomarker and risk stratification
Acute pain	Optimal treatment strategies	Coordination of care with outside providers	Barriers, skills and attitudes of ED providers	Biomarkers and risk stratification
Palliative care	Use of life-sustaining therapies	Disposition pathways/ follow-up care	ED and community hospice partnership	Larger cohort studies

[a]Acute dyspnea and spinal cord syndrome were also among the acute events discussed

the cancer. Twenty-six participants representing the fields of emergency medicine (8), oncologic (3), internal medicine (1), oncologic EDs (4), operations (1), and palliative care/ emergency medicine (3) were invited to the workshop. Representatives from the National Cancer Institute (4), the National Institute of Nursing Research (1), and the Office of Emergency Care Research (1) were also in attendance and participated in the discussion. The results of this one day workshop have been published [4]. Table 69.3 shows some of the research recommendations from the workshop (not an exhaustive list) (https://epi.grants.cancer.gov/events/emergency-medicine/).

This 1-day workshop led to the formation of CONCERN. Currently, more than 20 medical centers are represented. Membership is open to new members interested in collaborative research in cancer and emergency medicine. There are no membership requirements [52].

CONCERN objectives include: (1) identify knowledge gaps in the emergency care of cancer patients and define the scope, (2) accelerate knowledge generation and translation through multicenter research collaborations across oncologic and emergency medicine, (3) expand knowledge around treatment of oncologic emergencies in the emergency medicine setting, (4) translate research findings into national guidelines and community emergency care settings, (5) develop collaborative educational efforts in the area of cancer and emergency medicine, and (6) provide mentoring and consultation to new and established investigators working in the area of cancer and emergency medicine.

The first project included a multi-institutional prospective data collection which has been completed. The results have been published [7, 8], with additional publications currently ongoing. Periodic meetings via teleconference allow members to pursue collaborative projects and potential funding mechanisms are discussed. To date, plans are underway for a workshop at the National Institutes of Health campus in 2020. The goal of the workshop is to provide a 5-year research progress update, set new/revised research priorities, and establish new research collaborations at the intersection of cancer and emergency medicine. Priority Setting Questions to be addressed within each session include:

1. What are the gaps in knowledge/science around prevention and management of cancer-related emergency department visits?
2. What are specific research questions to address these gaps?
3. What are the resources, collaborations, and support needed to move this science forward?

Program in Oncologic Emergency Medicine (POEM), Department of Emergency Medicine at MD Anderson Cancer Center

Established in 2010, MD Anderson's Department of Emergency Medicine (DEM) is the first academic department in a comprehensive cancer center dedicated to the development of oncologic emergency medicine as a distinct discipline. The department's vision is to be the premier resource for education, research, and clinical care in the emerging discipline of oncologic emergency medicine. DEM presents a unique and exciting opportunity for exploring areas of research to improve the care of cancer patients and to identify gaps in current diagnostic and treatment approaches. The emergency center provides emergent and urgent treatment for MD Anderson patients and for employees and visitors injured on the MD Anderson premises. Every day, the emergency center provides service to approximately 70 patients with cancer-related conditions and is a vital safety net for MD Anderson patients. The emergency center features 44 rooms, including those designated for isolation, cardiovascular emergencies, and gynecologic emergencies. It is staffed by Department of Emergency Medicine physicians, mid-level providers, registered nurses, patient-service coordinators, and patient-care assistants.

In 2015, the MD Anderson Program in Oncologic Emergency Medicine was established to improve patient

outcomes by providing an interdisciplinary research hub that serves as a framework for developing emergency care research and implementing research-driven practice in caring for cancer patients who present in the emergency center. The Program integrates existing and newly developed research initiatives, with reduction in oncologic emergencies as its primary focus.

The Program's mission is to improve the care of patients with cancer and to reduce their need for emergency care during survivorship. Its vision is to be a locus for promoting evidence-based multidisciplinary and translational research in oncologic emergencies for a broad spectrum of clinicians and researchers across the institution and beyond. The Program is highly complementary to the disease-specific and treatment-specific centers at MD Anderson, none of which support specific research in oncologic emergencies.

Program Goals

POEM's program goals are to (1) facilitate the conduct of synergistic and collaborative projects focusing on oncologic emergencies, (2) develop and train physician scientists and graduate students in oncologic emergency research, (3) accelerate knowledge generation and synthesis by bringing together clinicians and scientists from diverse disciplines, and (4) establish synergy with existing centers and departments at MD Anderson.

To Facilitate Synergistic and Collaborative Projects Focused on Oncologic Emergencies

MD Anderson offers a breadth of resources to the Program, ranging from existing research and clinical databases, a large patient population, a substantial "core" support infrastructure, and multifaceted, experienced faculty. Publicly available databases can augment institutional data repositories.

Data Repositories Program researchers can capitalize on existing databases within the department and institutional data sources, including genomics, tumor registry, pharmacy, bioinformatics and biostatistics, and radiology and laboratory data, along with patient demographic, disease, and treatment data. The Program links these various databases together to create a powerful, comprehensive repository of personalized patient data (Fig. 69.1). Research protocols approved by MD Anderson's Institutional Review Board facilitate data collection and analysis. For example, prior to MD Anderson's adoption of Electronic Privacy Information Center (EPIC) for patient data across the institution, a locally developed database (the Zero G/Whiteboard) was utilized for collection of ED patient data. It included, for example, demographic information, body mass index and weight loss, type of cancer, primary and secondary presenting symptoms (chief complaints), number and frequency of emergency visits, symptom severity, and final disposition (e.g., admitted to hospital or discharged home). These data were linked to other institutional databases (see Fig. 69.1).

To Develop and Train Physician Scientists and Graduate Students in Oncologic Emergency Medicine Research

PubLab and Manuscript Advancement and Development Group (MAD): POEM's objectives were to build the literature in oncologic emergency medicine to improve patient care, and to build upon the expertise of DEM clinical faculty as thought leaders in this new discipline. There is a dearth of EM faculty trained in research. "Pub-Lab" was created as a

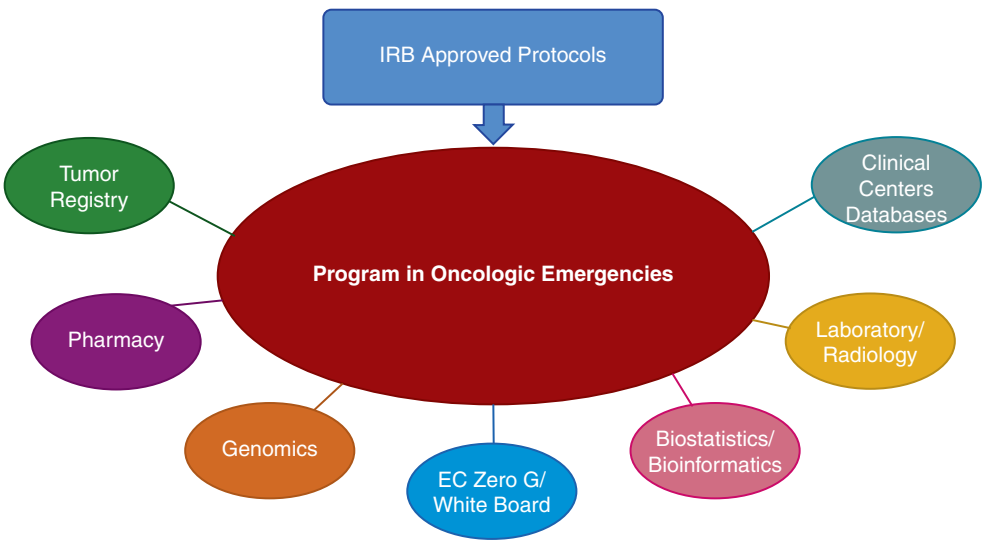

Fig. 69.1 Data repositories. The Program in Oncologic Emergency Medicine (POEM) databank links existing databases within the department and institutional data sources, including genomics, tumor registry, pharmacy, bioinformatics and biostatistics, radiology, and laboratory data, along with patient demographic, disease, and treatment data, to create a powerful, comprehensive repository of personalized patient data

series of regular meetings where the faculty discuss research articles, bring research ideas, or work in progress for publication. A faculty member trained in research provides guidance, and to optimize mentoring time, "mass-mentoring" groups were formed with each group comprised of faculty who are interested in a subject area/topic. MAD has up to four faculty and a mentor. Published studies from this group mentorship are in Table 69.2.

To Accelerate Knowledge Generation and Synthesis by Bringing Together Clinicians and Scientists from Diverse Disciplines

POEM builds upon existing scientific platforms, including scientific conferences and meetings both at local and national levels. January 2020 was the 7th Oncologic Emergency Medicine Conference at MD Anderson. Sponsored by DEM, among the aims of the conference was to fill the knowledge gap in oncologic emergency medicine by providing information in an interactive forum to enhance the decision-making of healthcare providers. Faculty from diverse disciplines served as speakers including the faculty in DEM. Each year includes presentations on innovative cancer therapies, e.g., immune checkpoint inhibitors, its related side effects and treatment, and management of immune-related adverse events were the highlights for 2020.

To Establish Synergy with Existing Centers and Departments at MD Anderson

As of October 20, 2020, there were 8,128,524 cases of COVID-19 in the United States with more than 218,986 deaths (and rising) [53]. Perhaps, one of the most lethal viruses, SARS-CoV-2, which causes COVID-19, has both an alarming contagion spread and disease severity that often requires emergency care. Our understanding of SARS-CoV-2 infection is rapidly evolving, with its clinical presentation and management barely understood. Cancer patients are expected to be particularly vulnerable to CoVID-19, given that their immune defenses are often deficient or compromised. Early and late toxicities from cancer treatment experienced by cancer patients also add complexity to their care. With little known about COVID-19, research of COVID-19 patients presenting to the ED was quickly established in DEM, and a protocol was immediately developed and obtained approval from the Institutional Review Board. Developing a protocol and a research project allowed for a cohesive method of collaborating with the different centers and departments at MD Anderson and provided synergy and a multidisciplinary approach (radiologists, oncologists, hospitalists, infectious disease) to understanding how to provide care to cancer patients with COVID-19.

Future Directions

Despite the continued rise in the number of cancer patients and the increasing complexity of cancer treatment, there is a dearth of research on oncologic emergencies even for disease complications that have been a concern for decades (acute pain, acute dyspnea, etc.). We have illustrated a couple of research efforts that created opportunities for research collaboration and engaged experts from many disciplines and institutions. Moreover, we also illustrated how the creation of a program in one academic cancer center has facilitated a timely response to research opportunities surrounding the COVID pandemic, for example. In recent years, transformative advances have emerged in the use of innovative therapies for cancer patients (immune therapies, gene therapies, gene editing, etc.). These approaches are some of the most promising treatment modalities but with unknown side effects or complications to the cancer patients. Because many cancer therapies are provided on an outpatient basis, the ED provides a safety net for cancer patients. The provision of care for those who present to the ED has to be guided by evidence.

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COVID-19

70

Knox H. Todd

Introduction

As of November 17, 2020, the World Health Organization reports 54,771,888 cases of COVID-19 worldwide and over 1,324,249 deaths [1]. The cumulative death total in the USA is almost one-quarter million [2]. Despite the promise of an effective vaccine in 2021, new cases and deaths may double in the coming months [3]. In addition to this toll, livelihoods have been destroyed, poverty rates and food insecurity are rising, and even our ability to gather with loved ones is curtailed.

Sadly, the USA has fared much worse than other developed countries during the pandemic. Basic public health measures to contain the COVID-19 epidemic (e.g., social distancing and mask wearing) have been interpreted as political acts in a highly polarized country. It is hoped that scientific reason will inform future developments in the USA, not the least to protect the most vulnerable among us, including those with cancer.

Longstanding inadequacies of our public healthcare systems and declines in longevity and well-being among US citizens have become more glaringly obvious during the pandemic, as has evidence of racial/ethnic disparities, driven by structural racism and workplace exposure to SARS-CoV-2 [4, 5].

In the midst of the pandemic, with rapid and ongoing changes in recommendations for management and the likelihood that a vaccine is forthcoming, it is difficult to discuss treatment issues with confidence in a traditional textbook. Alternatively, readers are directed to the large number of up-to-date online resources for guidance on current evaluation and clinical management (e.g., CDC, WHO, etc.). This chapter will briefly review real and potential impacts of the COVID-19 pandemic on the emerging field of oncologic emergency medicine. Among other questions, we will review COVID-related risk factors and health disparities, impact on treatment and cancer care systems (including cancer prevention, research, and economic effects), workforce mental health issues, and advances in emergency department (ED) palliative care.

Epidemiology

Cancer patients are at high risk for severe COVID-19 for a number of reasons. Age, obesity, and smoking are common risk factors for both cancer and COVID-19 morbidity and mortality. Advanced cancer causes declines in functional status (another risk for poor outcomes) and anticancer therapies alter immune responses to viral infection [6].

Giesen et al. recently reviewed risk factors for severe COVID-19 disease among cancer patients [7]. Patient-related factors included higher age, male sex, higher ECOG scores, the number of comorbidities, and smoking [8–14]. Cancer-related risk factors included a history of cancer [15], hematologic malignancies vs. solid tumors [10, 11, 16–21], lung cancer vs. other solid tumors [22], active cancer [9, 17], metastatic cancer [8, 22], and cancer treatment within 4 weeks of COVID-19 disease onset [23–25]. In addition, lymphopenia and granulocytosis were associated with an increased risk of severe disease or death [8, 13, 18, 25–27]. Whether cancer is an independent risk factor for poor outcomes in patients with COVID-19 is unclear at this time.

Initial reports from China by Liang et al. suggested that COVID-19 patients with cancer had higher rates of ICU admission and death; however, at the time of their publication, the investigators had evaluated only 18 patients with cancer from a cohort of 1590 subjects [28]. A subsequent study using propensity matching compared 232 adult cancer patients to 519 non-cancer controls admitted with COVID-19 to 9 area hospitals in Wuhan, China [8]. Over an approximately 1-month follow-up period, those with cancer were more likely to experience severe disease (64% vs. 32%) and death (20% vs. 11%). Risk for disease severity and death were greatest for patients receiving recent chemotherapy

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(within the past 2 weeks). In addition to known clinical risk factors for poor outcomes, the investigators identified a number of novel risk factors for disease severity among cancer patients, including advanced tumor stage, elevated tumor necrosis factor alpha (TNF-α) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), and decreases in CD4+ T cells and albumin-globulin ratios. They recommended heightened attention to infection control procedures during treatments, considering delays of adjuvant chemotherapy or elective surgery in endemic areas (with continuation of oral medications), and intensive risk stratification for patients with cancer and COVID-19, using the above identified biomarkers.

A study of 105 cancer patients and 536 without cancer admitted to 14 hospitals in Hubei Province, China, reported a higher risk for multiple poor outcomes (i.e., disease severity, ICU admission, mechanical ventilation, and death) among those with cancer [22]. Patients with hematologic, lung, or metastatic malignancies were at higher risk, as were those undergoing surgery vs. receiving only radiotherapy.

A more recent study performed COVID-19 surveillance among 1081 consecutive patients with solid tumors receiving treatment with intravenous, subcutaneous, or intramuscular agents at the National Cancer Institute of Milan (The COVINT Study) [29]. They found that over 2 months of epidemic spread in Milan, only 11 patients (1%) had confirmed, and 73 (6.7%) suspected, COVID-19. They concluded that when protective measures were followed in administering chemotherapy, COVID-19 contraction rates in cancer treatment facilities were relatively low.

A subsequent analysis comes from the LEOSS (Lean European Open Survey on SARS-CoV-2-Infected Patients) Study registry, in which a retrospective cohort of 435 cancer and 2636 non-cancer patients were assessed for COVID-19 morbidity and mortality [30]. For 435 cancer patients identified at the time of COVID-19 detection, progression to severe disease was seen in 55% and ICU admission in 27.5%, with a COVID-19-related mortality rate of 22.5%. Male sex, advanced age, and active malignancy were associated with higher mortality. After adjusting for confounding factors, mortality rates for those with and without cancer were similar. Despite this finding, cancer patients *as a group* are at higher risk of poor outcomes, as they are older and tend to have multiple comorbidities.

Analyses of UK Coronavirus Cancer Monitoring Project data provide more specificity for cancer as a risk factor for poor outcome. Investigators found that all-cause case fatality rates for patients with cancer who were hospitalized for COVID-19 rose with increasing age and the presence of hematologic malignancies [21]. After controlling for age and sex, those with hematologic malignancies receiving recent chemotherapy had an approximate doubling of mortality risk (OR 2.09, 95% CI 1.09–4.08).

Health Disparities

For the USA, COVID-19 represents the latest chapter in the long and tragic history of national health disparities. The pandemic has focused attention on persistent inequities experienced by US subpopulations facing persistent and collective discrimination (e.g., specific racial/ethnic groups and those of low socioeconomic status). As is true historically for other communicable and non-communicable diseases (e.g., tuberculosis, pellagra, HIV), to address the COVID-19 pandemic, we must understand its differential impact on these groups and focus our efforts to ensure more equitable monitoring and treatment, incorporating what we already know about the social determinants of health [31].

Current observational studies provide abundant evidence of disparities in both risk and outcomes for COVID-19. In retrospective cohort studies within a Louisiana integrated-delivery health system, researchers found that while Blacks comprised only 31% of those they served, 77% of those hospitalized were Black, as were 71% of those who died [32]. The authors note that in addition to a higher incidence of COVID-19 risk factors (e.g., obesity) among Blacks, most service workers in New Orleans and surrounding areas are members of minority groups, with many service sector occupations related to food preparation and serving.

Similarly, an analysis of data from Sutter Health, an integrated California healthcare system, found that among 1052 confirmed COVID-19 cases, after adjusting for age, sex, comorbidities, and income, Blacks were 2.7 times as likely as Whites to be hospitalized [33]. The authors posited that Blacks were more likely to be tested at a later stage of illness, as evidenced by their testing occurring more often in hospital EDs than in office or clinic settings.

In an observational cohort study of 2186 US adults with invasive cancer and COVID-19, Rivera et al. found that while remdesivir was associated with improved outcomes, Black patients were approximately one half as likely to receive this therapeutic agent as Whites [34]. Of note, remdesivir is most often administered within a clinical trial. Although an observational study, these findings suggest that racial inequity, particularly as related to clinical trial enrollment, continues to influence COVID-19 treatment.

Using publicly available datasets, Tirupathi et al. reported that Black and Latinx COVID-19 incident rates were disproportionately higher than their population percentage in 14 states and 9 states, respectively, and that while Blacks constitute 13.4% of the US population, they accounted for 22.4% of COVID-19 deaths [35].

Geographic disparities are also important to consider in the context of the COVID-19 pandemic. Initial waves of the virus impacted predominantly urban areas; however, the disease is now widely distributed in the USA, with less densely populated parts of the country experiencing disproportionate

levels of hospitalization and death. Rural health disparities result from multiple factors: poor access to healthcare (e.g., higher levels of the uninsured, long travel distances, lack of public transportation, poor Internet connections, lack of specialty care) and lower socioeconomic status (e.g., higher unemployment, lower median household incomes, lower proportions with post-secondary education), among other factors.

Dr. Robert Rodriguez, an emergency physician recently named to President-Elect Biden's COVID-19 Advisory Board, recently wrote of his experiences in volunteering to care for critically ill patients in his hometown of Brownsville, Texas, contrasting it to his current work environment in San Francisco: "My experiences over the past 2 months have shed light on another disparity—the enormous differential in emergency and critical care physician surge capacity between cities with robust medical academic institutions and communities that are situated far away from large medical schools" [36]. As part of his critique, he noted the bureaucratic barriers (e.g., credentialing paperwork, malpractice insurance) to urban physicians volunteering to serve in rural COVID-19 hot zones.

In rural and urban areas, for many of those with low-paying service jobs, social distancing or telecommuting are not options, and adverse social determinants of health are a large factor in observed COVID-19 health disparities [37]. This poor state of affairs is exemplified by the title of a recent JAMA editorial discussing COVID-19: "Failing Another National Stress Test on Health Disparities" [38]. While health disparities were widely recognized before COVID-19, the pandemic has served to highlight their importance and further focus our attention on this ongoing national tragedy.

Treatment

As noted in the Introduction, we will cover treatment issues in only a cursory fashion. Given the time interval required for publication, recommendations made today are likely to be misleading by the time this text is available. As a recent review of COVID-19 emergency medicine response noted: "When we are practicing at the bleeding edge of a viral pandemic that didn't exist 6 months ago, practitioners are often forced to work with less than robust data sets" [39]. Our readers are best referred to online sources from emergency medicine, oncologic, and federal/state organizations for the latest updates on evaluation and treatment.

In terms of management lessons learned during the pandemic, EDs have met multiple challenges involving isolation protocols and staff safety, patient/provider education, public health reporting, staff and space allocation, and communications – not to mention the widely publicized (real and potential) shortages of personal protective equipment and ventilators – as well as varying policy recommendations from federal, state, and professional authorities. Screening and testing criteria also evolved over time, as did criteria to justify hospital admission.

However, EDs, in part due to past experience with previous mass casualty incidents and epidemics, adapted rapidly to enhance surge capacity. They established separate "hot" and "cold" zones for COVID and non-COVID care, respectively, and in some cases, utilized separate tent and drive-in facilities to further segment care and augment capacity. In particularly stressed areas, adaptions could be primitive (e.g., using bandannas or handkerchiefs and plastic trash bags as a substitute for sophisticated personal protective equipment) [40]. Social media-driven efforts were conducted to raise funds for PPE in order to ameliorate inequalities in supply distribution As voiced by one emergency physician, "I think it should not have required a social media presence of health care workers, and for health care workers to get sick and themselves die from coronavirus, in order for hospitals to have received the standard equipment that they deserve" [40].

One of the most difficult decisions, and one for which lessons continue to be learned, surrounds questions of oxygenation and intubation. The risk of spreading viral-laden droplets and aerosols during oxygenation and intubation procedures complicates decision-making. In addition to standard protective equipment, powered air-purifying respirators (PAPR) are commonly used to reduce these exposures [41]. With more vigorous non-invasive oxygenation efforts, patient positioning techniques ("proning") [42], and recognition that tolerance of low patient oxygen saturation levels ("happy hypoxemia") can occur [43], intubation procedures are often delayed. ED airway management has improved markedly over the past decades and the COVID-19 experience is likely to further improve and standardize our airway practices [44]. Figure 70.1 presents an algorithm from NorthShore University HealthSystem intended to reduce aerosol exposure risk and maximize alternative oxygenation strategies for COVID-19 [39].

Pharmacologic approaches to both ED and oncologic patients continue to evolve. Beyond remdesivir, corticosteroids, and anticoagulants, the potential roles of convalescent plasma, monoclonal antibodies, antivirals, interleukin and cytokine blockers, histamine antagonists, kinase inhibitors, and protease antagonists in COVID-related disease management remain unclear [45]. The ED's place in future vaccine distribution systems over the coming year(s) is, as well, unclear; however, there is no doubt that emergency care providers will be among the first recipients of any new vaccines.

Cancer centers have also adapted rapidly to the challenges of treating vulnerable and potentially immunocompromised patients in the midst of a viral pandemic. Broom et al.

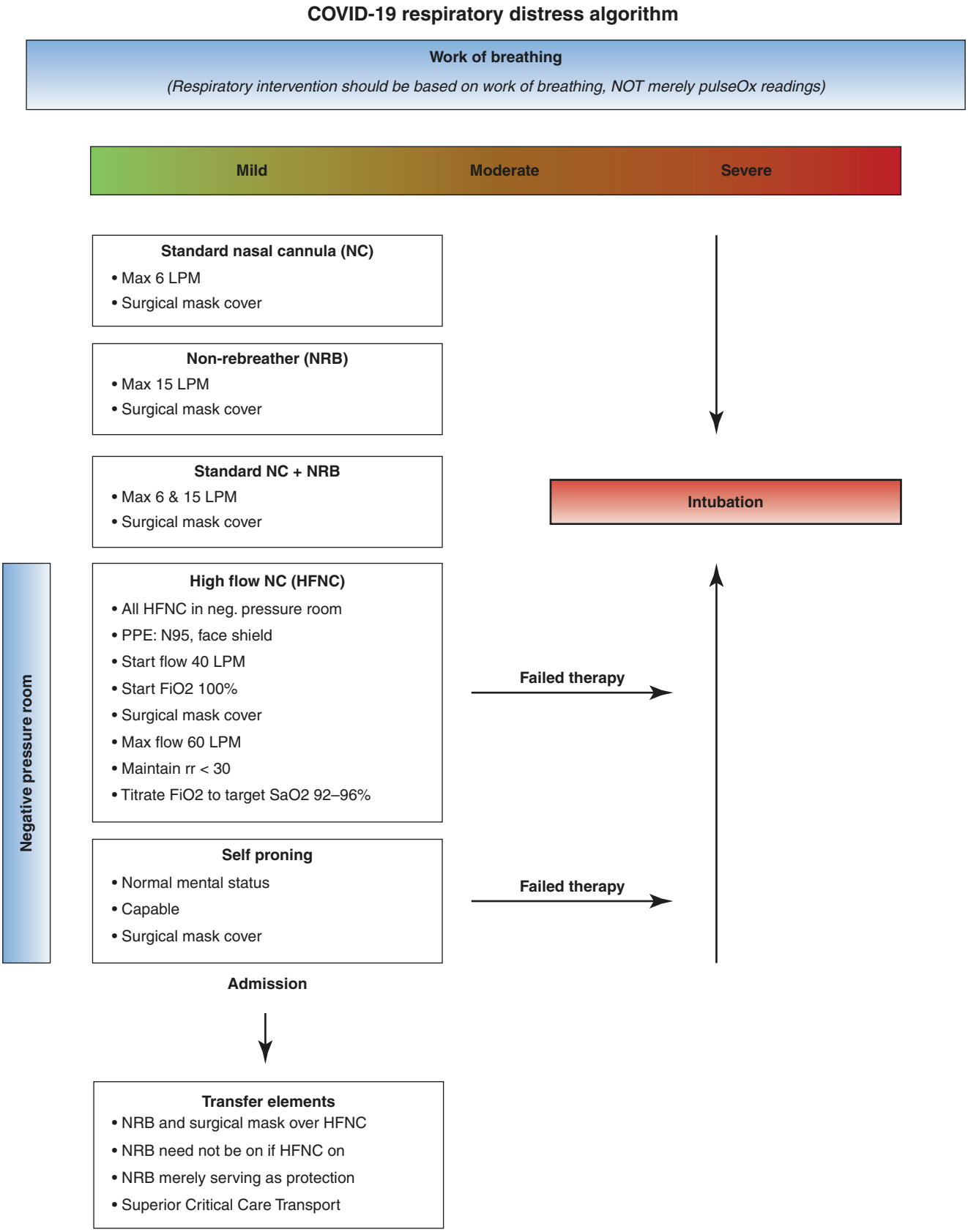

Fig. 70.1 Example COVID-19 resiratory distress algorithm. (From Leiker and Wise [39] with permission Elsevier)

recently provided an excellent review of modifications in cancer care resulting from COVID-19 [46]. In their review, they recognize that rapidly implemented responses to the pandemic may result in enduring changes to the cancer care system (for both better and worse). They touch on key principles to consider in understanding and managing such broad changes, including: (1) recognition that a return to "business as usual" after the pandemic is unlikely, (2) safety for patients and staff is a priority, (3) the pandemic requires a heightened focus on the negative consequences of immune-altering therapies, (4) the need for rapid evaluation of changes in practice, (5) ramifications (both interpersonal and economic) of increased telemedicine use, and (6) increased scrutiny of value of life assessments in the context of limited resources, particularly for the elderly, patients with palliative care needs, and those with multiple comorbidities.

Percival et al. reviewed early modifications of care for particularly fragile patients with hematologic malignancies served by the Fred Hutchinson Cancer Consortium [47]. Their overarching goal was to balance the risks surrounding the underlying hematologic malignancy and its treatment (often involving myelotoxic and lymphotoxic therapies) with evolving understanding of COVID-19 morbidity and mortality.

Aside from stringent infection control measures (i.e., strict control of access to healthcare sites, increased use of telemedicine, limiting the physical presence of caregivers), they increased their emphasis on oral and/or outpatient options, choosing therapies that reduce the risk for bone marrow toxicity and deferring therapy, if possible. There was also a marked reduction in clinical trial participation and a more nuanced calculation of risk-benefit for experimental therapies. Increased use of granulocyte colony-stimulating factor (G-CSF) and antibiotic prophylaxis was emphasized in an attempt to limit febrile neutropenia, as were stringent transfusion thresholds (given decreased donor availability), increased use of anti-fibrinolytics to decrease risks of spontaneous bleeding in thrombocytopenic patients, and delayed therapy for patients with positive coronavirus tests, when possible.

Given limited testing capacities, they proposed screening asymptomatic patients for coronavirus only prior to planned procedures, inpatient admission, stem cell transplant (HSCT), and chimeric antigen receptor (CAR)-T cell therapy. Finally, as in the ED, they increased attention to early discussions of patient and family goals of care, encouraging frank assessments of risk for those with limited expectations of benefit from more aggressive therapies. The ongoing reevaluation of cancer regimens in the COVID-19 era, with potential de-escalation of therapy when appropriate, holds the promise of more cost-effective, patient-centered care in the future [48].

A summary of general consensus measures [48] taken in response to the pandemic by seven comprehensive cancer centers in Europe is presented in Table 70.1. These measures are specific to a particular point in time in the evolution (as well as our understanding) of the pandemic and they will, no doubt, change over time.

Throughout the healthcare system, efforts to respond to the challenges of COVID-19, particularly in the context of cancer care needs, have had both positive and negative consequences. In prioritizing our response to the epidemic, certain aspects of cancer care have necessarily been deprioritized, occasionally resulting in suboptimal or delayed care.

Indeed, medical lawsuits in Spain may have resulted from delayed diagnosis and treatment of cancer during the pandemic [49]. The story noted that while hospitals were focused on COVID-19 treatment, cancer and other serious illnesses might have been neglected. While Spanish prosecutors are investigating such cases, physicians interviewed for the article stated that their overwhelming workload makes such errors inevitable, and specifically that when forced to rely on telemedicine only to evaluate patients, their ability to detect cancer will necessarily suffer.

In April of 2020, Denise Grady of the *New York Times* reported similar instances of COVID-19 collateral damage, in the story of a 53-year-old male with a hematologic malignancy whose death may have been caused by delays in chemotherapy due to COVID-related shortages of blood products. The article cited an American Cancer Society Cancer Action Network survey conducted at the beginning of the pandemic reporting that one-half of cancer patients and survivors experienced some impact of the pandemic on their care [50]. The survey found that 27% of patients in active cancer treatment report treatment delays, with 13% reporting no knowledge of when treatment might be rescheduled. Fully 40% of those in active treatment expressed concern regarding their ability to receive adequate care.

System Impacts

Healthcare system stresses (e.g., lack of surge capacity) and altered patient behaviors related to the pandemic (e.g., avoiding ED and office visits) are likely to lead to delayed cancer diagnoses at later stages and with poorer outcomes. Early data in the pandemic era reveal dramatic drops in cancer-related patient encounters. London et al. examined patient encounter data from 21 healthcare institutions (20 from the USA and 1 from the UK) and reported a 57% decline in US cancer-related visits and a 50% decrease in UK visits due to the pandemic [51]. Patient visits for new cancer incidence declined by 74% and 65%, respectively. They also report profound decreases in screening for breast (89%) and

Table 70.1 General consensus measures taken by cancer centers in response to COVID-19

Category	Measure
Hospital wide	Construct a hospital-wide crisis team responsible for coordinating measures between departments
	Encourage patients not to arrive early. Offer to text patients when you are ready to see them, so they can wait outside or in the car
	Instruct patients not to visit the hospital if they have symptoms indicative of possible COVID-19 (unless urgent attention is required)
	Call patients the day before planned hospital admissions, to discuss the presence of any COVID-19-related symptoms
	Screen patients at the entrance for symptoms of COVID-19 and fever
	Quickly isolate patients with COVID-19 in specialized departments, with the intent of relocation to regional collaborating hospitals (if possible)
	Reduce preclinical research activities to a bare minimum
	Stop patient inclusion for clinical studies or trials requiring additional actions and/or visits. Consider a tumor type-specific "exception list" of particularly successful studies for which inclusion continues
	Discuss each patient with a multidisciplinary team to consider alternative treatment modalities with the fewest visits or lowest capacity problems or that are the shortest in duration
	Therapeutic adjustments (versus regular guidelines) should be discussed in a multidisciplinary team meeting
	Conduct multidisciplinary team consultations remotely if possible or include only one representative of each discipline to limit the number of people participating in the meetings
	Inform patients about a possibly increased risk associated with anticancer therapy during the COVID-19 pandemic
	Enable telephone or video consultations for healthcare professionals who need to self-isolate
	When postponing procedures or contact moments, anticipate future capacity problems
	Do not prescribe corticosteroids as anti-emetics (if avoidable), and limit their use in patients treated with immune-checkpoint blockade, to reduce vulnerability to COVID-19
	With each patient, discuss resuscitation status to anticipate future decisions about intensive care
Outpatient clinic	Critically triage second opinions
	Do all follow-up appointments by phone (except when physical examination is necessary)
	When possible, reduce or delay the number of radiological-response evaluations
	Prioritize oral or subcutaneous treatments above infusion-based treatments to reduce time spent in the hospital
	Perform blood tests outside the hospital (e.g., at a general practice or at home), when possible
	Have oral medications delivered to the patient's home, rather than being picked up at the pharmacy
Day care	Consider omitting supportive treatments (e.g., no bisphosphonate infusion, except in the case of hypercalcemia)
	When possible, organize the administration of intravenous maintenance treatments at home
	When administration at home is impossible, consider temporary breaks or reductions in the frequency of intravenous maintenance treatments for less-aggressive metastatic cancers on a per-patient basis
Radiotherapy	Consider hypofractionated regimens for patients with limited additional benefit of regular regimens
	Create capacity for radiation as replacement of surgery
Surgery	Consider postponement of surgeries with high morbidity and mortality during the pandemic
	Consider other treatment modalities with equal benefit (e.g., radiation for prostate cancer, curative chemoradiation for other tumor types, or brain irradiation for metastases)
Others	Consider outsourcing of interventions (e.g., follow-up endoscopies) to private clinics

From van de Haar [48], with permission Springer Nature

colorectal cancer (85%). The impact of deferring cancer treatment and screening is difficult to estimate, and it is unclear how long these visit levels will remain depressed; however, it seems likely that we will see future increases in delayed cancer diagnoses and later-stage cancer presentations to the ED.

With regard to trends in radiology use, Norbash et al. examined imaging volumes in six US academic medical systems and a large national private practice consortium. As expected, they reported large decreases (40–70%) during early stages of the pandemic, with the largest decreases occurring in screening mammography and bone density scanning [52]. Interestingly, in discussing a pandemic-induced increase in telecommuting by radiologists, they noted the potential for a new source of tension between frontline and remote healthcare workers, stating that: "An unfavorable byproduct of radiologist distancing at work and by telecommuting may be the impression of radiologists utilizing technologists, nurses, and residents as human shields while maximizing radiologists' physical perimeter. The optics are potentially damaging in the long term for the larger radiology team beyond radiologists and may counteract loyalty and high-performance interdependence" [52].

This sentiment above reflects a possible negative consequence of the move toward telemedicine; however, COVID-19 continues to foster the dramatic growth of such virtual care. In part, this impetus derives from reductions in both practice regulations and reimbursement barriers [53]. As part of the US federal stimulus package passed in March of 2020 (The Coronavirus Preparedness and Response

Supplemental Appropriations Act or CPRSA), rules surrounding reimbursement for telemedicine were substantially relaxed [54]. Prior to CPRSA, CMS only reimbursed telehealth services when patients received care in urban or rural locations with a known health professional shortage. Recipients must also have had a prior established relationship with the physician, a limited number of services were covered, and only certain HIPAA-compliant platforms were allowed. After CPRSA, these requirements were loosened and CMS specified that telehealth services would be reimbursed at the same levels as in-person services. Private insurers generally followed suit, thus the use of telemedicine skyrocketed.

While the virtual delivery of medical care has many positives, there are, of course, negative consequences. In physically distancing ourselves from patients, we may also distance ourselves emotionally [46]. We have discussed how an inadequate assessment might lead to failures of diagnosis, but there are also failures of rapport- and trust-building between patients and clinicians that might be increased by use of virtual interfaces. Geographic and socioeconomic inequities in Internet connectivity may also serve to increase health disparities. It is possible that the popularity of telemedicine among providers and patients will sustain its current levels of use; however, it is also possible that future reductions in reimbursement, in addition to anti-competitive medical market forces, will counterbalance this trend.

With regard to cancer research, the COVID-19 pandemic has caused profound disruption. Most clinical trials were suspended, while the research enterprise has shifted its focus to pandemic-related themes. Many NIH-supported research programs were allowed latitude to shift in scope toward COVID-19 research with federal encouragement [55]. At the same time, there has been a drastic reduction in cancer-related philanthropy. As only one example, the American Cancer Society projects a $200 million (25%) decrease in donations over 2020 [56].

This disruption in the research enterprise does have a potential upside. As cancer research efforts pivot toward COVID-19, they may allow a more precise assessment of treatment toxicities and outcomes. As van de Haar and colleagues have outlined, four research priorities should drive current efforts: (1) to collect real-world data on how adjustments and de-escalation of treatment impact patients; (2) assess symptomatic and asymptomatic COVID-19 among those receiving chemotherapies, targeted therapies, or immune-checkpoint inhibitors; (3) develop epidemiologic models to estimate the cumulative incidence of COVID-19 among those with cancer within a specific timeframe; and (4) estimate COVID-19 morbidity and mortality in patients with cancer who are treated with chemotherapy, targeted therapy, immune-checkpoint blockade, and/or G-CSF [48]. COVID-19 thus provides a unique opportunity to focus on the impact of treatment de-escalation, which for ethical reasons might otherwise be difficult.

Prevention

As noted above, the pandemic has caused large shifts in our ability to maintain current cancer care practices. At the national level, both the Welsh and Scottish governments suspended breast, cervical, and colon cancer in March of 2020, while Northern Ireland suspended screenings 1 month later [57]. In the USA, the Centers for Medicare and Medicaid Services lowered the priority for cancer screening programs at the outbreak of the pandemic [58]. Patient fear of exposure to the virus also served to decrease rates of cancer screening.

Tobacco prevention programs have experienced a similar COVID-related deterioration. Tobacco consumption has likely risen during the pandemic at the same time that access to healthcare has been disrupted. It is thus likely that tobacco-related morbidity and mortality will rise over the coming months and years [59]. Smokers are of particular interest, as the pandemic may both increase smoking behaviors in some (due to boredom and lack of social contacts during quarantine) and decrease such behaviors in others (due to a desire to maintain health in the face of external threats) [60].

Smoking may also impair the ability to utilize masks effectively (envision a mask dangling around the neck surrounded by cigarette smoke plumes) and increase mucous membrane viral exposure through contaminated fingers, while encouraging smokers to be outdoors (perhaps thereby decreasing exposure risk). Fewer visits to smoking cessation resources may mean a drop in use of nicotine patches and smoking cessation medications. Compounding these issues, medical care for chronic smoking-related conditions has been curtailed. Consistent with these expectations, EDs have indeed reported fewer admissions and delayed admissions for myocardial infarction and stroke since the pandemic began [61].

Surprisingly, initial reports suggested that smoking might have a protective effect against COVID-19, given that the prevalence of current smokers among hospitalized patients in China was unexpectedly low [62]. A cross-sectional analysis of patients presenting in New York City with COVID-19 found that smoking was not a risk factor for critical illness, and that it might even serve as a protective factor for hospital admission [63].

As another example of screening trends, Murray et al. report large reductions (as much as 58%) in referrals to Irish dermatologists for evaluation of pigmented skin lesions at the height of the pandemic [64] (Fig. 70.2). Interestingly, they also reported decreases in Internet searches (as a proportion of total searches) for both skin cancer and melanoma,

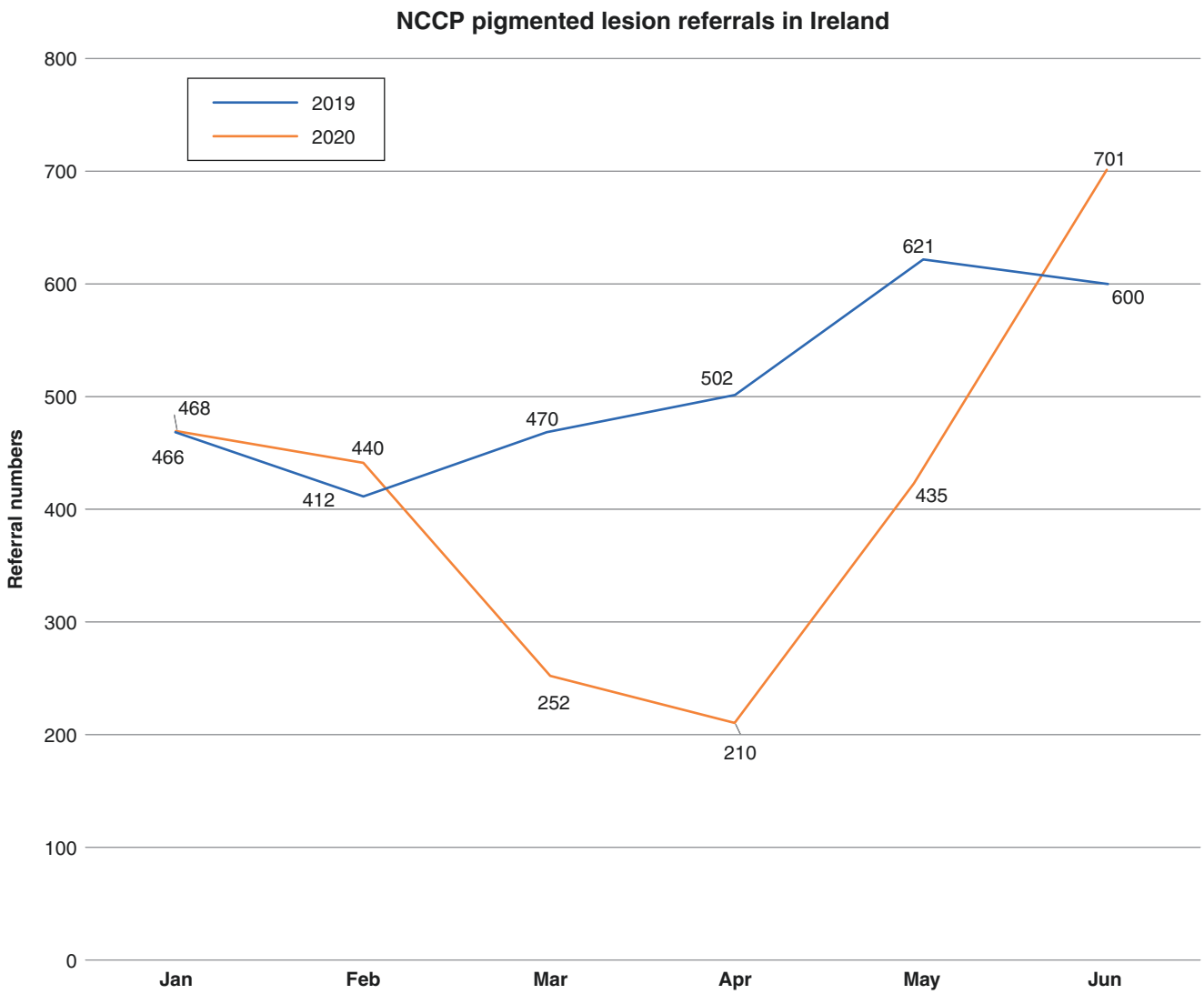

Fig. 70.2 National pigmented lesion referrals recorded from the NCCP Ireland during 2019 and 2020 of the months of January to June. (From Murray et al. with permission John Wiley)

as COVID-19 search activity swamped all other terms. Earnshaw et al. note similar declines in skin cancer referral (as much as 56%) [65]. They also make the valuable point that data regarding declines in cancer detection rates will assist in planning for the inevitable increase in diagnoses (often at later stages of disease) that will occur during any eventual pandemic recovery stage.

Economic Considerations

During the early months of the pandemic, while the numbers of COVID-19 visits to US EDs increased, the total number of ED visits plunged dramatically. Figure 70.3 illustrates this fall in patient volume for both academic and community EDs in one Massachusetts system [66] and others report similar findings [67, 68]. Data from the National Syndromic Surveillance Program show that national ED visits declined by over 40% during the early months of the pandemic, with the steepest declines among children and females and in the Northeast [69].

The public avoided the ED if possible, given the graphic images of ED chaos depicted in the media, the fear of contracting the virus, and a desire to avoid overburdening the system. In addition, while the public remained at home, injury rates outside the home (e.g., traffic injuries) decreased and fewer communicable diseases (other than COVID-19) required emergent care.

With this decrease in ED visits, the number and proportion of lower-acuity presentations fell, as did the need for a number of non-critical (and highly reimbursed) ED procedures. Most subspecialties experienced a fall in ED consulta-

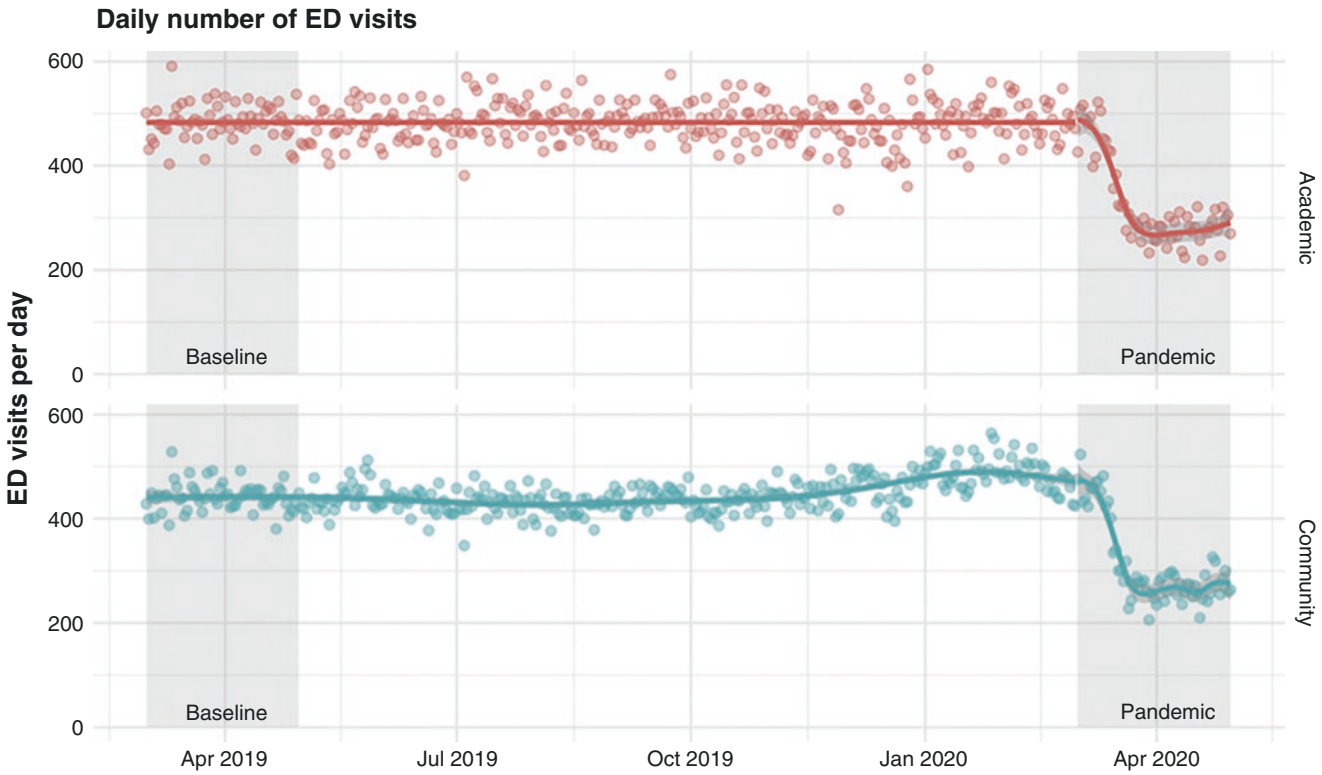

Fig. 70.3 Daily number of ED visits over time across the five included hospitals, separated by academic and community hospitals. (From Baugh et al. [66], with permission Elsevier)

tions, as well. Given that many hospitals cancelled elective surgeries and other procedures, the rate of ED visits for post-procedural complications declined in a similar fashion.

Case Study

Your sister, a 58-year-old breast cancer survivor and her spouse decided to take a rafting trip with two other couples. Before traveling, they decided to obtain tests for coronavirus and drove to a nearby free-standing ED where their nasopharyngeal samples were taken. The results were subsequently negative and they very much enjoyed the trip with friends.

Your sister's spouse paid $150 in cash for testing while your sister gave the clerk her insurance card. Two weeks after returning from vacation, she received a bill for $5000, leaving her responsible for substantial charges that the insurer did not cover. She leaves a message for you with her story and asking how such a discrepancy in charges is possible. How do you explain this?

Fortunately, you remember that the New York Times *has published a number of articles by Sarah Kliff on the issue of surprise medical billing* [70, 71]. *Surprise billing occurs when billing services used by "out-of-network" emergency physicians or other clinicians seek payment directly from patients when there is a gap in coverage. Patients often have no knowledge (or way of knowing) that this might occur when seeking care in the midst of an emergency. The issue has been festering for years without resolution; however, given increased attention to billing issues during the pandemic as well as the economic crisis, it is likely to be resolved by legislation that will ultimately decrease payments to physicians and EDs.*

After a quick review, you understand that wide variations exist for similar services, even in the same geographic area. Variations exist for a number of reasons, but the underlying reason is that the government does not regulate healthcare prices. Each facility negotiates with a number of insurers, and patients served by smaller insurers tend to pay larger bills. Those patients whose insurers have not negotiated with the charging entity may be responsible for the entire amount of the charge and these fees can be enormous. This can occur when a patient is served by an out-of-network provider, either the entire facility or an individual physician (e.g., *emergency physician, anesthesiologist), who is providing services as an independent contractor and charging separately.*

In coping with surprise medical billing for coronavirus testing, Sarah Kliff offers a number of recommendations [71]*: (1) obtain your test at a public site (e.g., state, county, or city-operated), (2) use your primary care physician or a*

federally qualified health clinic, (3) avoid hospitals and free-standing EDs (these locations charge facility fees, which are substantial).

While ED visit rates have more recently waxed and waned with pandemic trends, the impact on emergency physician and hospital finances has been overwhelmingly negative. Telemedicine use has expanded, replacing the need for many ED and office visits, and thus far, regulation of telehealth continues to be relaxed with many restrictions on reimbursement lifted. It is difficult to know whether these trends will continue, but to the extent they substitute for lower acuity, privately insured, and more profitable ED visits, emergency physician compensation is likely to fall [72]. The trend toward fewer high-margin ED visits may portend less need for emergency physicians and ED closures in low-margin settings, both urban and rural.

In its long-running biannual national survey of US physicians, the Physicians Foundation focused exclusively on the pandemic [73]. In the first of its three-part survey, conducted from July 15–26, 2020, they report that 8% of physicians (estimated to represent approximately 16,000 medical practices) had closed their practices permanently because of the epidemic and 43% have reduced their office staff, with 72% reporting loss of income and 59% expecting that COVID-19 would lead to a reduction in the number of independent practices in their communities. Similarly, a September 2020 survey of primary care practitioners found that 54% have furloughed employees and 28% have permanently reduced staff; 19% report that clinicians have retired early; and 15% state they are leaving (or planning to leave) their practice. Such losses in community-based medical practices will only increase stresses on ED capacity.

Cancer centers, particularly larger centers with a national or international clientele, have experienced large declines in service demand and face large pandemic-related economic losses. As in other parts of the healthcare system, the declines are in patient encounters that tend to be more profitable, as care moves out of the hospital and elective procedures are postponed or cancelled. In addition to patient fears of viral exposure, many patients who would seek cancer care nationally or internationally are electing to remain near their homes for treatment. Parking garages (a large source of income for many centers), restaurants, hotels, rental services, and the travel industry at large are all experiencing losses related to cancer center business turndowns.

The pace of economic recovery at these centers after the pandemic is an open question. It seems likely that cancer patients will be less willing to travel such great distances if care is available locally, and cancer treatment services have become more dispersed geographically over time. When seeking cancer care out of state, costs for travel, lodging, and lost wages alone are estimated to be double that for in-state care [74]. The disruption and suspension of many clinical trials during the pandemic will also lead to economic losses that may be slow to recover.

Workforce Mental Health

Emergency medicine practice is stressful. Our specialty has long recognized the intense nature of our practice and the challenges it poses to its practitioners. Among medical specialists, emergency physicians experience one of the highest rates of burnout. Emergency physicians suffer from practice-related anxiety, depression, and depersonalization with some frequency [75].

COVID-19 has only heightened these issues, particularly in areas of early pandemic spread. Studies of Chinese healthcare workers found high rates of mental distress for those involved in the COVID-19 response; moreover, emergency providers experienced the greatest risk for multiple negative outcomes [76]. During the pandemic, particularly in the New York area, emergency physicians faced staff, space, and personal protective equipment shortages. Clinical practice was conducted in an atmosphere of crisis, and emergency physicians often found themselves treating friends and colleagues. Initial reports estimated a 46% emergency physician seroconversion rate (admittedly using a limited sample of physicians from at a single New York ED) [77]. A deluge of news from around the world heightened a sense of emotional and social crisis. Physicians often responded to institutional mandates that were delivered without a sense of consent. Contradictory guidelines regarding PPE were a particular source of anxiety. Would I contact the disease? Would I infect my family? Not surprisingly, it is predicted that our specialty will experience an increase in anxiety disorders and PTSD as a result of COVID-19 [78].

To better quantify COVID-related stress among emergency physicians, Rodriguez et al. conducted a cross-sectional survey among academic emergency physicians from seven EDs [79]. The 426 respondents reported high levels of anxiety for themselves and their families. In terms of measures to relieve this anxiety, they desired more widely available PPE, rapid coronavirus testing, and clear communication regarding ED protocols related to COVID. Providing more specificity, Wong et al. outlined a number of practical initiatives, both individual and administrative, to combat mental distress within the emergency medicine workforce (Table 70.2) [80].

Table 70.2 Potential solutions for COVID-19-related emergency provider stressors, ordered by Maslow's hierarchy of needs

Maslow's level of need	COVID-19 concerns	Recommended strategies
Level 1: Physiologic (e.g., food, sleep, physical and mental health)	Extra workload demands around COVID-19 preparation and treatment Physical strain of protective equipment (dehydration, heat, exhaustion) Housing needs during isolation/quarantine periods Inadequate or disrupted sleep patterns Physical symptoms of COVID-19 disease for healthcare workers who contract the virus	*Individual* Time for basic bodily care and refreshment/relaxation and stress-management breaks Avoid maladaptive behaviors with negative physiologic effects (e.g., excessive alcohol, prescription drugs) Physical health and fitness (exercise programs, walking outside, mobile applications) Online mental health technologies (telepsychiatry, mobile applications, PTSD coach) *Administrative* Provision of respite for staff members requiring isolation (e.g., housing, childcare) Supplementation of readily available water and nutritious food while on clinical duty Careful attention to individual work schedules to maximize rest and sleep between shifts Facilitation of testing and treatment for individuals who develop symptoms or become ill Virtual wellness and information town halls Early and confidential recognition, detection, and referral for treatment of psychiatric symptoms (e.g., cognitive-behavioral therapy)
Level 2: Safety (e.g., personal security, financial security, resources)	Fears of personal safety around infection and lack of adequate personal protective equipment Lack of clarity around viral transmissibility (airborne versus droplet) Concerns for job security and potential debt, especially if an individual becomes infected with COVID-19 Feelings of being undersupported and underequipped to provide safe care	*Individual* Peer consultation and supervision of PPE donning/doffing *Administrative* Alternative strategies to produce/distribute PPE (local manufacturers, donations, recycling) Clear and consistent messaging and shared decision-making with healthcare workers regarding infection rates, risk, and strategies to minimize risk Contingency plans for healthcare workers who cannot work during quarantine period or if they fall ill after contracting COVID-19 to provide job and financial security without negative consequences
Level 3: Love and belonging (e.g., friendship, family, social connectedness)	Possible separation from family members Risk of exposure to loved ones, especially those who are at high risk Physical isolation from friends, colleagues	*Individual* Increase peer social support with regular contact with colleagues, family, and friends Seek out and share social support virtually *Administrative* Acknowledgment and affirmation of healthcare worker stressors and concerns Creation of specialized collaborative partnerships or teams focusing on COVID-19 Online-based group support networks and mental health checks Resources for significant others and family members of healthcare workers to support their loved ones during epidemic
Level 4: Esteem (e.g., respect, status, self-determination/control, fairness)	Pressure to serve as source of definitive information for nonmedical family and friends Constant pressure to maintain clinical acumen with increasing volume and acuity Ethical challenges in triaging resources (ventilators, staffing, bed capacity)	*Individual* Limit worries to actual (rather than anticipatory) threats Foster a spirit of patience, fortitude, tolerance, and hope Channel concerns through productive output (scholarly efforts, peer coaching, teaching, educational materials on COVID-19) *Administrative* Create specialized ethics teams/protocols for information and mentorship in decision-making Use patient-centered resources for difficult decisions Highlight exemplary behavior and celebrate individual contributions and efforts Create clear, transparent, fair, equitable, and accessible policies

(continued)

Table 70.2 (continued)

Maslow's level of need	COVID-19 concerns	Recommended strategies
Level 5: Self-actualization (e.g., desire for higher achievement)	Tension between public health priorities and individual patient care Advocacy for larger system changes to minimize the effects of the epidemic	*Individual* Focus on efforts within one's individual control Accept situations one cannot change Contribute to productive efforts for change *Administrative* Sharing of information across institutions/systems Peer mentorship for clinical, administrative, and academic duties related to COVID-19 Creation of volunteering, innovation, and service opportunities to support response efforts (e.g., creation of new devices/tools, clinical strategies)

From Wong [80], with permission Elsevier

Palliative Care

Emergency physicians encounter patients with unmet palliative care needs during almost all clinical shifts [81]. Given that the majority of hospital admissions originate in the ED, critical and timely decision-making by emergency physicians often determines the subsequent intensity and trajectory of treatment for life-limiting illnesses, including intubation and intensive care utilization. During the COVID-19 pandemic, questions of medical futility and appropriate goals of care have become more prominent and efforts to address unresolved palliative care issues have received increasing attention.

Early in the pandemic, the University of Washington implemented an institution-wide plan to address COVID-19-related palliative care needs [82]. Focused on the ED, the intensive care unit, and acute care services, it provided strategies to identify goals of care, manage distressing symptoms, and support family members. In the ED, the palliative care service conducted daily huddles with staff, provided consultations for patients with poor prognosis and at risk for intubation or CPR, supported implementation of DNR orders when appropriate, and embedded a palliative care specialist to screen patients. The palliative care service also provided telephonic coaching and support 24 hours/day, 7 days/week.

In responding to the early surge of COVID-19, New York-Presbyterian Columbia University Irving Medical Center developed a psychiatry-palliative care liaison team (including trainees) to provide ED palliative care services [83]. During the peak of the epidemic, this service provided a 24-hour coverage for palliative care needs, allowing emergency providers to better meet the overwhelming demand for medical care and establishing a model to provide future surge capacity. For 110 ED patients seen by the palliative care team, the median age was 81.5 (range 46–101), two-thirds were community dwelling, and few presented with advance directives or Medical Orders for Life-Sustaining Treatment (MOLST) [84]. Ninety-one of 110 patients (83%) were considered "full code" on arrival to the ED, falling to 20 of 100 (18%) after the initial ED palliative care consultation.

In a qualitative study, emergency medicine researchers interviewed representatives from 52 hospitals in the USA to identify ED-palliative care innovations driven by the pandemic [85].

Table 70.3 summarizes these innovations in systems, staffing, and technology. Respondents reported that such innovation was welcomed by clinicians and positively impacted patient care trajectories.

Conclusions

In this brief review, we have discussed a number of challenges posed by the COVID-19 pandemic and its impact on the evolving subdiscipline of oncologic emergency medicine. Beyond direct negative outcomes due to infection among our patients, we are concerned that degradation of our screening and prevention efforts, in addition to pandemic-related barriers to appropriate cancer treatment and research, will have long-lasting effects well into the post-pandemic era. At the same time, the pandemic has exposed faults within the healthcare system and society that, when recognized and confronted, hold the promise of a better future.

In the USA specifically, the politicization of science, with its long and dark history, has become increasingly overt. This anti-science effort must be resisted and counteractions taken against it by physicians, researchers, and cancer patients. The stark evidence of health disparities associated with COVID-19 should give rise to further efforts to reduce and eliminate such inequities. Given resource constraints posed by the virus, our health systems have an opportunity to re-examine the consequences of overly aggressive cancer therapies, as well as the inferior provision of palliative care. A necessary redesign of our cancer care system in response to COVID-19 has many lessons for the larger healthcare system and society at large.

Table 70.3 Summary of innovations in ED palliative care

Type of innovation	Example of innovation	Innovation detail
Model of care delivery	Embedded PC clinician in the ED	PC clinician seated in the ED dedicated only to ED consults
	Strengthened ED presence	Achieved through daily rounding, EMR chat function
	Mobile PC consult service	Dedicated service focused on ED and ICU needs
Staffing	PC attendings with extenders	Residents with focused GOC or ACP training
	PC attending with PC fellows	Triage cases based on complexity to appropriate clinician
	PC extender with psychosocial partner	Pair volunteer non-PC physician with social worker or child life specialist who perform all consults together
Technology-enhanced PC-ED	Off-site tele-PC	Centralized team of either RNs or PC physicians for all hospitals in a health system
	Blended on-site tele-PC	Triage patients based on their capacity to engage to either in person or tele-PC
Primary PC training and education	Trainings and tools	COVID-specific conversation training; collated resources (with apps, Google Docs, provided laminated cards)
Case identification and task stratification	Proactive case identification	Remotely screen ED track board, daily rounding
	Formal triggers (for primary PC or specialty consult)	Automated or manual – encompassing age, marker of underlying illness, marker of acute illness
	Focused, abbreviated consults	Task-oriented consults focused on specific patient needs
	Nursing-initiated consults	Consults to PC triggered by nursing staff using clear trigger criteria

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The Physician and Cancer: In Their Own Words

71

Marshall T. Morgan, Patrick J. Crocker, Burton F. Dickey, Sherry-Ann Brown, and Knox H. Todd

Introduction

The word, "cancer" is, in itself, a powerful term that should never be underestimated. It carries a certain shock value – a sense of doom and gloom that seems qualitatively different from other diagnoses. This is as true for physicians as it is for laypersons. In this collection of prose and poetry, four physicians tell us stories of their cancer experiences, with the goal of communicating what matters. We hope these illness narratives help our readers care for themselves and for others in a more human, and humane, manner.

Editor's Note

Marshall Morgan was my mentor and friend. He headed the UCLA emergency medicine program where I trained, and throughout our careers we met frequently to share stories of our lives, usually over a meal and always over a glass of bourbon. By example, Marshall taught me the importance of empathy. Professionally, one of the things I most admired in Marshall was that although he was generally the smartest person in the room, you didn't realize it until later. The day after he felt the first symptoms of cancer, Marshall took time to write the words below. These were included in his memorial service a short time later.

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The Difference a Day Makes

Marshall T. Morgan, MD (1941–2015)

Yesterday morning thinking about my future I made the reasonable estimate that I would live in a functioning active state into my mid-to-late 80s (I am 73). I considered: When should I retire (not now: my wife is still working and I like my job)? On the other hand, I spend too little time with my children and grandchildren, so maybe sooner than later.

Last night, I developed an unusual RUQ pain with a strong pleuritic component and no tenderness. I consulted my physician and we decided I should go to the ED. The ED workup, which would have taken a week as an outpatient but was done in 4 hours, revealed a large number of liver lesions and a mass hugging the lesser curvature of the stomach.

Today, unlike yesterday, I am contemplating a much shorter future for myself (disappointingly I have young grandchildren). I will undergo EGD tomorrow in an attempt to get a tissue diagnosis and soon will face the question of chemotherapy, whether to undergo chemotherapy.

As an emergency physician I have been the messenger to others on the day that made the difference. Some, like the 60-year-old gentleman with a large palpable right upper quadrant mass, were not surprised at all, but resigned. Others whose imaging was done in the expectation of finding a gallstone or kidney stone were shocked as I was. Interestingly, when there were tears, it was family members, not the patient, who shed them.

I have shed no tears. Most of my thoughts have been around changing the expectation of my remaining life span and hoping that I will be spared severe pain and disability

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for some time, so I can enjoy my family, my friends, and this wonderful planet to the greatest extent possible before I leave them behind.

M.T.M.

February 5, 2015

Los Angeles

(Reprinted with permission from Jean Marie Campbell-Morgan)

Editor's Note

Pat Crocker is a true pioneer of emergency medicine in Central Texas, having served as Chief of Emergency Medicine at both Austin's Brackenridge Hospital and later, Dell Children's Medical Center. He now lives in Kerrville, Texas, and recently published two books of stories from his rich career [1, 2]. On reviewing his second book: *More Letters from the Pit: Stories of a Physician's Odyssey in Emergency Medicine*, I wrote:

> …Pat Crocker captures the stories of our lives as emergency physicians. These accounts of the highs and lows in caring for patients over his remarkable career are delivered in often stark, and occasionally grim, terms. Physician readers will recognize these stories immediately, if not as their own, then as those that might have been. For readers with a non-medical background, reading these pages opens a rich window into the human theater that is emergency medicine. For our families and loved ones, reading this book will help you understand why we might be less talkative than usual when returning from a long clinical shift. My hope is that after reading this book, conversations about our work become easier. At times tragic, at times humorous, More Letters from the Pit conveys a profound understanding of the gratitude we owe our patients and a sense of wonder at the mysteries of chance and providence that bring us together in the crucible that is the modern emergency department [2].

Thomas J.

Patrick J. Crocker, DO

I have found that some of the great saves are not those accompanied by that adrenalin rush of the ER we in the field seem to crave. No blood and guts. Instead they're ones fighting foes that threaten to kill your patient from the inside out. Cases that require thought, planning, an engaged patient, and a whole team of multidisciplinary players. These kinds of saves can roll out over months and the ending uncertain for years. But they are no less gratifying than the others.

I first met Thomas as Marcia and I prepared to build our new house. We had decided on polished concrete floors, and our builder who referred us to him thought he was the best in the business. And so we drove out to meet him, see his shop, and let him show us some samples of his work.

The shop was located out on a country road. Rather an informal place surrounded by beautiful old oak trees and, of course, displays of his handiwork. We walked around a bit and saw no one, so went inside to the office area. No one there either. "Hello," I called out. And then a little shuffling from a back room and he emerged from behind a curtain.

He smiles and says hello. A firm handshake. He's about my height, fit, slender, and rangy. I can tell by looking at his sloping shoulders and biceps he works for a living. And obviously doesn't think concrete work is enough exercise so he hits the weights regularly too. He seems a bit rough around the edges. I suspect he likes to party, ride motorcycles, and an occasional bar scuffle may not be beyond him. I like him immediately.

He's anxious to show us his craft and we walk around his shop seeing what he can do. He is a master. This guy turns concrete into something almost indistinguishable from marble. Creates beautiful concrete countertops, tabletops, and sinks. It only takes us a few minutes to agree this is our man and we tell him we'll let the builder know to call him.

The work on the house goes forth and I get to know Thomas better. He proves to be a very likeable sort. Smart, hardworking, and honest. A man of his word. After dealing with a few issues that cost him some profit, I thanked him for being one of the few honest folks in the construction business that I've ever met. We became friends over the months of building.

One day we're talking about medicine, my experiences at the trauma center, and he asks if I could be his doctor. He's a hardworking guy but without medical insurance so I said sure, but I can't see him at the ER. I told him I would do a physical, get some labs, and get him on the right track. He hadn't seen a doctor in a decade and it was past time. He agreed and I told him to call when he was ready. The physical would be in my office at the new house.

Months pass and I don't hear from him. I supposed the same distaste for doctors and health care that kept him away for a decade had not yet been overcome. And then a day later, the phone rings. He wants to know if I could have a look at his elbow following an injury. And I of course said come on over. And he does.

It's a sad conundrum for physicians to help patients like this. In my case, my malpractice insurance only covers me for cases in the hospital. I'll be going bare to help him out but he deserves it. I also trust him to believe that no matter what the result may turn out to be, I did my best. Nevertheless, we will have the conversation that my no-cost assistance comes with the agreement he forgo the right to sue me. I hate to

bring this up with someone I now consider a friend but I also have to protect my family. He will understand.

Thomas shows up a few hours later sporting his usual smile and laugh. He's still ten feet away but I can already see his elbow is a mess. He tells what he can remember of the incident, which isn't much. He was at the Burning Man festival and then woke up in jail. We both laugh. He says all he really knows is when he was released he found a police citation in his pocket. I laugh to myself at this one. Good luck, Nevada police, you'll probably never be seeing Thomas again. This is *pure* Thomas!

After I examine him I conclude he has probably torn part of his bicep insertion and wrenched the joint pretty badly. I get him set up with an orthopedist I went to medical school with. As he is captive in my office I ask him about that physical I was to perform for him. I say, "Dude, you're 50 years old and a smoker. We need to do this for you. Don't be a stupid shit and put this off any longer." We are obviously frank with each other. I also point out he won't be working for a while and it's the perfect time to go get that lab work done. And that I'll want a chest X-ray. I'm not going to take responsibility for a smoker's health at his age without one. He laughs his laugh and agrees, and the next day follows up as he said he would. Thomas is a man of his word.

Two days later all the lab work has returned and is normal. I didn't expect to find much but when a patient hasn't seen a physician in so long you never know. I also get unwelcome news.

One of the radiologists saw my name on the chest X-ray order and decided to call me directly. He spills the news that it shows a mass in his right lung and it looks like whatever it is has spread to the lymph nodes in the right side of the chest. This means most likely cancer and fairly advanced. This is horrible. I worry it's a death sentence for him.

I give him a call, trying not to alarm him but tell him what I have found. Bad news is something I dread giving patients. But we must deal with the facts. No exceptions. I tell him to head back to the radiologist for an enhanced CT scan of his chest. We'll try to nail this down as best we can as soon as possible. Thomas takes the news straight up. He knows I'm worried. I order a CT scan of his chest and he returns to the radiologist.

Late that afternoon the radiologist is on the phone again. He's confirming on the CT scan this appears to be lung cancer, spread to the lymph nodes on the right side. Even worse it appears to have involved the aorta. This may make the cancer inoperable, I fear.

Before I tell Thomas the bad news I call one of the oncologists I've known for years. I consider him one of the best and would trust him with my family members. We discuss the case and he isn't too hopeful. Statistically, he suspects a small cell carcinoma, too advanced for surgery, and a very low survival rate. I feel crushed for Thomas. He does add, however, that given his young age, he thinks we should go for broke on this one, try for a save. Not palliation where we might just try to give him some more time on earth but go for a straight-up cure. He asks me to send him over to the office.

A PET scan is ordered and the oncologist and I speak again. Yes, definitely a cancer. Thomas will now need a biopsy of the lesion to nail down the type and characteristics of the cancer. He again takes the news in a levelheaded fashion and then asks the question I dread. "How long do you think I've got Doc?" I hedge a bit, let him know it's not good news, but the oncologist wants to go for a cure. And Thomas is now determined to get that cure. I add one other thing, "You must quit smoking NOW. The oncologist says there's no hope if you keep smoking." He says he will quit today.

The rest of the story unfolds over the following weeks, pretty much as predicted. The biopsy confirms small cell carcinoma and the prognosis is not good. The big decision is what to do for Thomas. Surgical removal is not possible.

A patient's active involvement in their healthcare is something I treasure. I believe an active participating patient leads to better outcomes. Thomas and the oncologist talk over treatment options, all of which are aggressive. Thomas and I review everything. Before starting treatment Thomas wants to consult with some other specialists. I agree, but say, "Let's not waste a lot of time." We'll be thorough but I want to get things started. Thomas is making his survival his only project, tracking down every available approach. He even includes an herbalist. Checking into supplements that might increase his chance of survival or at least keep him healthier through the chemo process.

A couple of weeks pass as other consultants see him. He finds another very aggressive oncologist who wants to press for a cure also. The two oncologists disagree a bit on therapy, as they don't want to kill him during the process, but finally agree to take the chance. And so does Thomas. The goal is a cure if possible. A combination of chemotherapy and radiation that will begin immediately.

Through 5 rigorous months of therapy, including prophylactic brain radiation to kill any cancer cells hiding there, Thomas and I talk from time to time. I give him my encouragement. I learn he's still hanging in there, still determined despite feeling poorly. We talk about the predictable baldness, all the economic stress of this kind of major therapy, and the supplements.

Multiple PET scans and follow-ups occur. The tumor shrinks but remains visible on the scans. After a year, however, it hasn't progressed and we start to consider that maybe this is residual dead tumor and scarring. Another year goes by without any change and happily the tumor ultimately is considered dead. I'm elated for Thomas.

So this case had none of the adrenalin we ER doctors seem to crave. It was a very satisfying result nonetheless. The excitement of blood and guts substituted for a thorough approach by a great team of doctors and a very determined patient.

I am again convinced that fate plays a role in our lives. Also that thoroughness and an unflinching determination to cover all your bases from the start, every time, save patient's lives. As usual, all of the what if's churn through my mind. What if I had let Thomas's initial reluctance to skip the chest X-ray rule? Just entered a note, "Patient refuses chest X-ray at this time." Covered my ass with a simple note and left his hanging in the breeze. I just can't approach patients like that and glad I didn't.

I recall a patient I saw years before who presented with a complaint of a shoulder rash. On examination I found a very large melanoma lesion. I explained what was wrong and what we needed to do. She refused, saying she would treat the lesion with over-the-counter peroxide. We talked for about 15 minutes, me attempting to convince her that peroxide treatment was not only ill-advised but would result in her death. She was adamant. Unbelievable.

And I entered that CYA, cover your ass, note in the chart, "Patient refuses referral for an apparent advanced melanoma despite counseling" and had her signed out against medical advice. A sad addition to her medical record. My ass was covered, but hers wasn't. I consider such encounters personal failures every time. I have failed to engage my patient in a fashion that led them to the appropriate care.

Thomas remains happy, healthy, and tumor-free. We talk once in a while. Someday when we're both motivated he'll give me some concrete finishing lessons. We'll build a tabletop together.

And though the danger of getting too close to your patient and their tragedy and crossing that line between empathy and self-preservation is one I wrestle with almost daily, sometimes you have to cross it for a friend.

Editor's Note

As a fellow chair at MD Anderson, I will always be indebted to Burton Dickey for his advice on managing my department within a byzantine modern cancer center and for his ever-quick wit and humor that sustained me through interminable administrative meetings. When I asked Burton to write about his experience with multiple myeloma (from which he is in remission and doing well), he told me: "Don't expect anything sentimental or melodramatic; that's not me. Just the facts." What follows is his advice on what to do (and what not to do) for physicians facing a cancer diagnosis.

Advice for a Physician (or Anyone Else) with Newly Diagnosed Cancer

Burton F. Dickey, MD

I was diagnosed with multiple myeloma 8 years ago and today am fortunate to be healthy and in complete remission. Quite a few physicians, including my friend Knox Todd, have asked what I learned. My advice comes down to three simple suggestions. First, read about your disease – a lot. Second, do what grandma told you to do – eat well, sleep plenty, and exercise. Third, know when to let go – more about that later.

When you are first diagnosed with cancer, it is likely to be a shock. Many cancers are diagnosed in someone without any symptoms on the basis of a test. Even when a symptom is present, the diagnosis of cancer as the underlying cause may not have been apparent. With the diagnosis, one's mind immediately goes to the questions of "How much time do I have left?" and "How good or bad will that time be?" In my case, the possibility of myeloma was identified by my cardiologist on a routine blood test as part of an annual visit to have my cholesterol-lowering statin medication adjusted. A complete blood count showed low hemoglobin, white cells, and platelets, indicating that my bone marrow was failing or being replaced by tumor or infection. I am fortunate to work at the MD Anderson Cancer Center and was evaluated later that afternoon by a hematologist friend, then referred for a bone marrow biopsy the next day. Some of the possible diagnoses had a fairly grim prognosis and others were not so bad. My mind raced through the possibilities until I received the diagnosis of myeloma with a sense of relief when the biopsy was read the next day. Of course myeloma can have serious complications such as renal injury and bone involvement, and it can have a poor prognosis depending on its genetic drivers, but it was more tractable than some of the other possibilities. I was fortunate to have a "low-risk" tumor genetic profile and no renal or bone complications and began standard-of-care treatment almost immediately.

My first piece of advice is to read. This is advice you are unlikely to need since you will be able to think of almost nothing else initially, and will be intensely interested in treatment options, prognosis, etc. Working as a pulmonologist in a cancer hospital, I had a superficial understanding of myeloma, particularly since the focus of my practice is on pulmonary complications (such as pneumonia, bronchiectasis, and obliterative bronchiolitis) of hematologic malignancies (including leukemia, lymphoma, and myeloma).

Nonetheless, I began to read deeply both the classical and cutting-edge literature of myeloma. I will never know as much as my oncologist, who has spent her entire career focused on myeloma, but I think my reading served both me and her well. In clinic visits, she could move quickly through the basics because I now knew most of them, and we could focus on more subtle questions. I believe that most physicians appreciate a knowledgeable patient for exactly this reason and, even when challenged, appreciate the possibility of thinking through a routine issue in a new light. In a few situations, my challenges led to a change in care. After about 2 months of reading almost nothing but the myeloma literature, I settled back into a more normal schedule of reading the medical literature with a focus on pulmonary and general internal medicine, but also with a particular eye out for new developments in myeloma.

My second piece of advice is to remember what grandma told you. Hopefully you already have good habits of eating, sleeping, exercising, and balancing work and home life. If so, I suggest continuing with little change, and if not, talking to your grandma about common sense habits. There is a lot of advice on the Internet about outlandish diets that can beat back cancer, but with little or no evidence to support them. I have always eaten three conventionally balanced meals a day, with dinner routinely eaten with my family, and we didn't change anything during most of my illness. After high-dose cytotoxic chemotherapy, nausea is a problem so supplementation with commercial nutritional drinks may be necessary transiently, but sticking for the most part with a routine balanced diet preserves one of life's pleasures and a foundation of good health. Sleep is similar – most of us know how beneficial a full night of sleep is and what the main components of good sleep hygiene are. Some excess fatigue resulting from cancer therapy is common, so a nap can be helpful. Possibly the most important area of lifestyle management during cancer treatment is exercise. Of course this is important throughout life, but cancer and its treatment can lead to debility and frailty, so every effort should be made to prevent that. Besides, it is my impression that regular exercise minimizes symptoms from treatment and improves mood. Work is another important issue. I have always derived great pleasure from work from its intellectual interest, the companionship of colleagues and patients, and a sense of contribution. Depending on the side effects of treatment, continuing to work at either a full or reduced level may be possible, and for me it was an ongoing source of stability and pleasure. While cancer obviously imposes a strain on one's family and friends, it can also draw them closer as an unexpected benefit.

Having talked about all the things you can do to contribute to your well-being in the first and second points, I'll now pivot and remind you that you can't do it all. Clearly, others will need to administer chemotherapy and radiotherapy and perform surgery. However, beyond that, there is a time to stop challenging the judgment of others or pushing yourself through difficult spots. For me, the most glaring example of knowing when (or when not) to let go was when I became septic during the neutropenia that followed high-dose chemotherapy and autologous hematopoietic transplantation. This was performed as an outpatient, and while it was a difficult couple of weeks, I was grateful to be in my own home with my wife as caregiver. However, late one night I developed lower abdominal pain and the urge to urinate every few minutes. I knew my neutrophil count was low, so it should have been obvious to head to the emergency room. Nonetheless, I experienced an irrational fear of a crowded emergency room in which I would end up feeling worse instead of better. When we finally went at 7 AM, I was quickly placed in a comfortable room in the emergency center; a compassionate colleague had taken a history, performed an exam, diagnosed diverticulitis, started antibiotics, and ordered placement of a Foley catheter that immediately relieved the urinary retention resulting from the diverticulitis. My experience of the rest of the hospital stay was equally caring and comfortable, and I've wondered in retrospect why I initially had such dread and delayed the obvious need for care. I suspect that part of it was due to clouded thinking from sepsis, but another part was probably an excessive desire for independence and reluctance to let go and be cared for by others. Thus, my third piece of advice is to recognize that while you can be a powerful agent in your own care, you can't do it all and it's important to trust the skill and good will of others.

In summary, I have been fortunate in my encounter with cancer, and hope that you are as well if it enters your life. I believe I did some things to aid my recovery, but also a few things that interfered, and hope you can learn from my experiences.

Editor's Note

Perhaps the most rewarding thing about editing a textbook is learning from your authors. In reading Dr. Sherry-Ann Brown's work in the area of cardio-oncologic, I was introduced to another facet of this poetic scientist's work. She has published a number of works exploring the more spiritual side of clinical practice, and two of her poems from *The Healer Speaks: Poems For Patients, Students, Doctors, Nurses, Therapists, & Everyone Impacted By Medicine* are reproduced below [3]. These poems speak to her personal relationship with cancer patients and give voice to the often-unspoken dialogue between patient and physician (of which neither may be fully aware).

Excerpts from *The Healer Speaks*

Sherry-Ann Brown, MD, PhD, FACC, FAHA

Somebody Tell Me

What will kill me?
When will I know?
When will I die?
What will I die from?
Is it cancer?
Is it heart disease?
Is it crossing the street?!
Somebody tell me!

Give me a disease of the heart.
What can I do?
How can I prevent this?
How can I fight this?
Tell me my risk of having heart disease.
At least then I could walk faster,
I could skip; I could jump; I could run!

I could eat better.
I could have my vegetables,
My fruits, and my fish.
I would even have my nuts,
And extra-virgin olive oil.

I would even stop smoking.
Well, I would try.
Because I would want to
Run away
From both cancer
And heart disease.

I don't know if I really could,
But I surely would try.
And I might even tell those around me
To try too.
We might even try together.
Maybe as a community,
We could do this together.
Tell me,
Tell us.
What is our risk of heart disease?
Tell us as a community.
Tell us as a population.

What can we do
As a team
To grow old together?
It's not so much about dying,
As it is about living.

How is it that heart disease
Kills more people
In this country
And in this world.
Than cancer?

Then why am I more afraid of cancer?

I suppose it's because with cancer,
It comes so soon!

Where did this cancer come from?
She's so young.
He's so young.
I am so young!
Why cancer?
Why me?
When will I die?

What will kill me?
How will I know?
When will I know?

Oh, the agony.
Breathe.
Just breathe.
Relax.
And live.
Truly live.
Love to live.
And give all.
Till it's time.

The Healer Speaks

The Healer Speaks
My dearest patient:
When I see the hurt in you,
I want to reach out
And wrap myself around you,
To protect you.
I cannot myself take the pain from you,
I cannot shield you from the damage
Of deterioration and injury.
Yet, when you hurt I hurt,
When you heal I heal.
You shouldn't hurt alone.
I am honored to hurt with you.
I am honored to hurt for you.

The Patient Speaks
My dearest doctor:
Do not hurt for me.
Do not hurt with me.
Let me hurt without you,
For my hurt is temporary,
And I will heal.
Whether physically,
Or perhaps spiritually.
I fear your hurt is irreversible,
And you may not heal.
While you protect me,
Who will protect you?
Since I cannot protect you,
How will you protect yourself?

The Healer Responds
My dear patient:
I suspect You are right.
Thank you for releasing me,
To protect myself too.
To care for myself too.
To heal myself too.
To gain healing
In the midst of others too.
Thank you for helping me see
That first I have to take care of me.

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Correction to: Endocrinology and Metabolism

Sai-Ching Jim Yeung

Correction to: Chapter 29 in: K. H. Todd et al. (eds.), Oncologic Emergency Medicine, https://doi.org/10.1007/978-3-030-67123-5_29

Figure 29.3 had three typographical errors in the figure label in the original publication of the book. This has been replaced by a corrected version of Figure 29.3.

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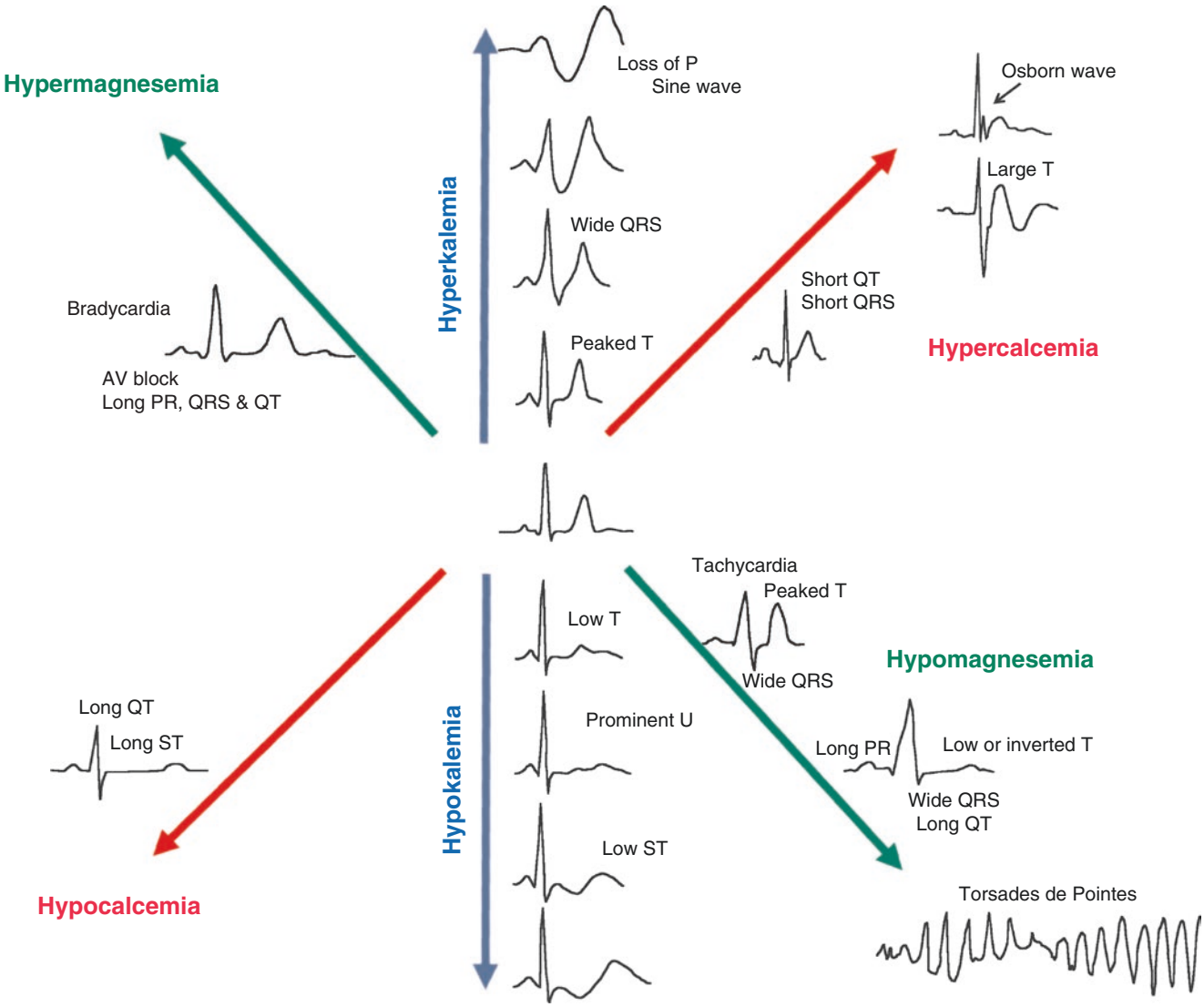

Fig. 29.3 EKG changes in the presence of electrolyte abnormalities

Multiple-Choice Questions

1. Patients with the following cancers have the highest incidence (of at least one) of ED visits within 1 year of diagnosis:
   (a) Breast, prostate, and melanoma
   (b) Pancreas, brain, and lung
   (c) Colon, prostate, and eye
   (d) Oral, melanoma, and endocrine
   (e) None of the above
2. Which cancers are associated with the most ED visits?
   (a) Lung, breast, prostate, and colon
   (b) Pancreas, brain, and lung
   (c) Leukemias and melanoma
   (d) Cervical, prostate, and breast
   (e) None of the above
3. Limitation(s) of using ED visit-level data to explore ED use by oncologic patients generally include:
   (a) Visit-level data may not be able to account for multiple visits made by the same patient
   (b) Visit-level data provides no information regarding the quality of care
   (c) Visit-level data cannot capture the incidence of ED use by all patients with cancer in a given sample or population
   (d) A and C
   (e) B and C
4. What is the most common method used to identify potentially preventable ED visits in cancer patients?
   (a) Ambulatory care sensitive conditions
   (b) The Billings algorithm
   (c) Panattoni's methodology
   (d) Prevention quality indicators
   (e) None of the above
5. Which of the following statements about ED use by oncologic patient is false?
   (a) Oncologic patients visit the ED across the cancer care trajectory.
   (b) Underlying symptoms and the diagnoses associated with an ED visit are considered *need*-related determinants of ED use.
   (c) Oncologic patients have lower rates of admission and lower rates of multiple ED visits than the general US population.
   (d) ED use by oncologic patients reflects a complex interaction of individual and contextual factors (e.g., provider behavior, health system characteristics, and health policies).
   (e) None of the above.
6. Which of the following data elements is not a HIPAA identifier?
   (a) Internet Web Address
   (b) Birthdate
   (c) Insurance plan number
   (d) IP address
   (e) Gender
7. What is the term for an information system that collects and analyzes data from a census of cancer cases?
   (a) Health information exchange
   (b) Electronic medical record
   (c) Cancer registry
   (d) Computerized physician order entry
8. Who do you want to identify first when designing an order set?
   (a) EMR analyst
   (b) Nursing
   (c) Patients
   (d) Users (i.e., physicians)
   (e) Clinical champion
9. A 34-year-old man smokes a pack of cigarettes when he goes out on weekends with friends. He has smoked more than 100 cigarettes in his lifetime. This man is best classified as a:
   (a) Current smoker
   (b) Daily smoker
   (c) Nonsmoker
   (d) Insufficient information to classify smoking behavior
10. A 58-year-old woman with chest pain is placed in observation status in the ED's chest pain center. She smokes 30 cigarettes daily. After several hours in the

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chest pain center, she becomes agitated and says she wants to walk out to the ambulance bay to smoke a cigarette. The most appropriate course of action is to:
(a) Offer her a nicotine patch
(b) Offer her a small dose of oral diazepam
(c) Have her sign out against medical advice
(d) Offer her a nicotine patch and 2 mg nicotine gum

11. Which of the following statements is true regarding ED-initiated tobacco control?
(a) Clinical trials have not demonstrated the efficacy of ED-initiated treatment.
(b) Nicotine replacement therapy and motivational interviewing have been shown to help ED smokers achieve abstinence.
(c) National bodies that accredit EDs and emergency medicine residencies require emergency care personnel to treat tobacco dependence.
(d) Although clinically effective, ED-initiated tobacco control is expensive.

12. A true statement about Screening, Brief Intervention, and Referral to Treatment (SBIRT) is:
(a) SBIRT was developed to facilitate the treatment of opioid-use disorder, then adapted to tobacco.
(b) SBIRT requires smokers to receive pharmacotherapy, such as nicotine gum or patches.
(c) SBIRT requires individuals with substance-use disorders to be referred to programs for post-ED care.
(d) SBIRT should be avoided for individuals with co-occurring serious mental illness or other substance-use disorders. These individuals should be referred to intensive outpatient programs.

13. When does alcohol use most commonly begin?
(a) Adolescence
(b) College-aged adults (18–22 years old)
(c) Middle aged adults
(d) Elderly

14. Which of the following types of cancers is *not* known to be linked to alcohol use?
(a) Breast
(b) Rectal
(c) Uterine
(d) Larynx

15. Which racial/ethnic group suffers from the highest rate of alcohol-attributable injury?
(a) Latino
(b) Asian
(c) Black
(d) Native American

16. Which diagnostic criteria for alcohol-use disorder was added to the DSM-5, from the DSM-IV?
(a) Tolerance
(b) Craving
(c) Legal problems
(d) Withdrawal

17. An extensively sun-damaged 60-year-old female presents after spraining her ankle. On examining the lower limb, you note a large very suspicious pigmented lesion on her calf. If you were to perform a skin biopsy to get a histological diagnosis, what would be the most appropriate?
(a) Punch biopsy of one edge
(b) Total excision of lesion with a 2-mm margin
(c) Shave biopsy of half the lesion
(d) Incisional biopsy of part of the lesion

18. Which of the following is *not* a high-risk melanoma phenotype?
(a) Red hair
(b) Multiple nevi (>100)
(c) Dark skin
(d) Pale eyes

19. What is the strongest predictor of melanoma mortality?
(a) Size in centimeters of the melanoma
(b) Breslow thickness
(c) Age of the person
(d) Age when it occurs

20. In the ABCDE mnemonic, which of the below is incorrect?
(a) Aggravating – really unsightly to look at
(b) Border – irregular
(c) Color – multiple colors
(d) Diameter – over the size of a pea or growing
(e) Evolution – changing over time in size or height

21. How long does HPV vaccine protection last?
(a) 5 years
(b) 7 years
(c) 9 years
(d) At least 10 years

22. What are the US recommendations for cervical cancer screening on age of starting and method?
(a) At the age of sexual debut, cervical cytology
(b) At the age of sexual debut, cervical cytology and HPV testing
(c) 21 years, cervical cytology
(d) 21 years, cervical cytology and HPV testing

23. In the United States, what types of treatments are recommended for CIN2/CIN3?
(a) Observation

(b) Ablation
(c) Excisional procedure (e.g., LEEP or CKC)
(d) Hysterectomy

24. What will happen with most women who become infected with HPV?
(a) Develop cervical cancer in 10 years
(b) Develop significant preinvasive disease in 5 years
(c) Have persistent HPV infection
(d) Clear the infection spontaneously within 18–24 months

25. A 65-year-old male presents to the ED with several days of progressive diffuse, colicky abdominal pain, with nausea, vomiting, and abdominal distension. He has been obstipated for several days and denies any rectal bleeding. He was diagnosed with ulcerative colitis and pancolitis 25 years ago. After his initial diagnosis of ulcerative colitis, he was maintained on chronic mesalamine therapy with infrequent flares of disease requiring short courses of steroids. He moved into the area 10 years ago and failed to establish contact with a local gastroenterologist. His last colonoscopy was over 10 years ago. In the ED, he appeared pale with a blood pressure of 95/60 mmHg, a heart rate of 110/minute, and temperature of 100.5 °F. Physical examination revealed a thin male in mild distress. On abdominal examination, he demonstrated a distended abdomen with diffuse tenderness and absent bowel sounds. Laboratory results show a mild lactic acidosis and decreased hemoglobin with normal LFTs. Plain films reveal a diffusely distended colon and small bowel with a point of transition in the sigmoid colon and absence of air distally. What is the most likely cause for this patient's diagnosis?
(a) Toxic megacolon
(b) Acute pancreatitis
(c) Ascending cholangitis with underlying primary sclerosing cholangitis
(d) Colon cancer
(e) Acute diverticulitis

26. The following symptoms of colorectal cancer are often suggestive of advanced disease, with the exception of:
(a) Large bowel obstruction
(b) Perforation
(c) Hematochezia
(d) Pneumaturia
(e) Abdominal pain or perirectal pain

27. A 53-year-old man presents to the ED with complaints of constipation and occasional blood in his stool. He has been told he has hemorrhoids in the past. Upon further questioning, he admits to a 10-pound weight loss and constipation with intermittent diarrhea. His only medication is aspirin and HCTZ. Orthostatics in the ED are negative and his rectal examination is positive for blood. Abdominal films reveal a preponderance of stool. Hgb is 11.5 with a normal MCV. What is the best next step?
(a) Admit for further workup
(b) Discontinue aspirin
(c) CT colonography
(d) Consult GI for outpatient colonoscopy

28. A 74-year-old woman with a recent diagnosis of colon cancer presents to the ED after being found by her daughter on the kitchen floor. The patient states she was eating and suddenly developed abdominal pain, became lightheaded, and fell trying to get to the telephone. Hip films in the ED reveal a right trochanteric fracture. On physical examination, the patient complains of right hip and right lower abdominal pain, and she appears to be guarding on her abdominal examination. Orthopedic surgery has evaluated the patient and want clearance to take her to the OR. What should the next step be?
(a) Obtain a cardiac risk assessment
(b) Upright abdominal series
(c) Larger bore IV and fluid resuscitation
(d) Oncologic evaluation

29. A 68-year-old male presents to the ED with large volume hemoptysis and respiratory distress about 18 months after radiation therapy for an early-stage primary lung cancer of the right upper lobe. A CT chest scan is obtained and shows a right upper lobe opacity unchanged from previous imaging and consistent with typical postradiation changes. No other airway abnormalities are identified. What is the best next step?
(a) Bronchoscopy to identify and isolate the bleed
(b) Bronchial artery embolization
(c) Thoracic surgery consultation for lobectomy
(d) Intubation, followed by bronchoscopy to identify and isolate the bleed

30. A 75-year-old male smoker presents to the pulmonologist with dyspnea during minimal exertion for 4 weeks. Spirometry showed reduced peak expiratory flow rates and moderate obstruction. A CT chest without contrast showed a large, tumor obstructing the left mainstem bronchus and causing collapse of the entire left lower lobe. When considering therapeutic bronchoscopy, what are the main features associated with improvement in symptoms?
(a) Greater dyspnea, good functional status
(b) Greater dyspnea, poorer functional status

(c) Minimal dyspnea, poorer functional status
(d) Minimal dyspnea, good functional status

31. An 81-year-old male with a history of advanced stage primary lung cancer of the right lower lobe treated with chemotherapy and radiotherapy presents for surveillance 1 year after treatment. On review of the CT, there appears to be a local recurrence of the tumor with growth into the right bronchus intermedius and complete collapse of right lower lobe. The tumor has completely invaded and destroyed the right lower lobe bronchi. Which one of the following factors is a predictor of successful therapeutic bronchoscopy?
(a) Presence or absence of necrosis
(b) Size and extent of endobronchial invasion
(c) Patency of the lobar bronchi distal to the obstruction
(d) Type of lesion (intraluminal, extraluminal, mixed)

32. A 62-year-old woman is undergoing rigid bronchoscopy under anesthesia for a bleeding tumor in the left mainstem. While the bronchoscopist is coagulating the surface of the tumor with argon plasma coagulation, the patient suddenly develops ventricular fibrillation and arrest. What is the rare but dreaded complication that could have caused this event?
(a) Idiosyncratic reaction to intravenous anesthetics
(b) Gas embolism from argon plasma coagulation
(c) Perforation of the left atrium
(d) Myocardial infarction

33. A 49-year-old man with retroperitoneal sarcoma on chemotherapy is in the ED with a 3-day history of abdominal pain, distension, and fever of 38.5 °C. His lactic acid is 4 mg/dL, and the blood pressure is 70/50 mmHg. He takes extended release morphine, 60 mg q12h and immediate release morphine. His absolute neutrophil count is 100/μL. He denies confusion. The triage nurse found that he was alert, and oriented x 3. His wife says he sleeps more and is withdrawn. She has not noticed agitation or hallucinations. You decide to reevaluate his mental status with the mini-mental status examination (MMSE). Which domain(s) of this test are most helpful to confirm hypoactive delirium?
(a) Orientation to time, place, and self.
(b) No specific domain is better than the other.
(c) The test will be unremarkable so the patient has no delirium.
(d) Attention/concentration (backward spelling or serial 7 subtractions and 5-min memory recall of three phrases).

34. A 62-year-old man with recent diagnosis of esophageal adenocarcinoma has arrived in the ED with acute onset garbled, nonsensical speech. Time of onset was 1 hour before your bedside examination, which reveals aphasia and right pronator drift. There is no history of atrial fibrillation, seizure, or migraine. CT of head shows no intracranial hemorrhage (ICH) or areas of vasogenic edema. EKG reveals sinus rhythm. His BP is 145/80 mmHg. You determine that the patient probably has an acute ischemic stroke in the left middle cerebral artery or one of its branches. There is no evidence of thrombocytopenia, active bleeding, or abnormal coagulation tests. The most important therapeutic decision at this point is to:
(a) Admit to the floor on telemetry and consult neurology to see later.
(b) Give ASA 81 mg stat and order MRI brain to confirm diagnosis.
(c) After a quick checklist to ensure there is no absolute contraindication and discussion with patient or proxy for consent, start IV thrombolytics or transfer to a dedicated stroke center for thrombolytic therapy.
(d) Start intravenous heparin and transfer to ICU.

35. Paramedics brought a 26-year-old woman who was found unresponsive in her bedroom. She has acute myeloid leukemia in relapse. Her mother said she had been complaining of headaches for 2 days. There are no signs of intentional or accidental drug overdose and no history of illicit drug use or suicidal attempts. She was intubated on the spot for airway protection. Her Glasgow Coma Scale score is 9, pupils measure 3 mm and both react to light, and bilateral Babinski reflexes are present. The paramedics report she has been seizing despite repeat doses of lorazepam (total of 4 mg). You witness the patient hyperventilate and arch her body, while the blood pressure rises from 100/75 to 190/110 mmHg, with bradycardia. Her pupils dilate for 15 seconds. She then returns to baseline. CT scan of brain showed an epidural hematoma with mass effect and acute hydrocephalus. This episode is more likely to represent:
(a) Convulsive status, refractory to benzodiazepines
(b) Nonconvulsive epileptic status
(c) Plateau wave
(d) None of the above

36. A 34-year-old woman with acute myeloid leukemia in relapse was found unresponsive. She had complained of headaches for 1 week. She was intubated and her Glasgow Coma Scale score is 9, pupils measure 3 mm and both react to light, and bilateral Babinski reflexes are present. She has been seizing despite repeat doses of lorazepam (total of 4 mg). You witness the patient hyperventilate and arch her body, while the blood pressure rises from 100/75 to 190/110 mmHg, with brady-

cardia. Her pupils dilate for 15 seconds. She then returns to baseline. CT scan of brain showed an epidural hematoma with mass effect and acute hydrocephalus. Laboratory studies reveal a platelet count is 45,000/μL and INR 1.25. The most important treatment sequence is:
(a) Start osmotherapy, replace coagulation factors, and emergently consult neurosurgery for hematoma evacuation.
(b) Supportive care only, get an EEG and transfer to ICU with antiepileptic drug therapy.
(c) Transfer to ICU and start osmotherapy. Consult neurosurgery to see later.
(d) Keep in the ED, start osmotherapy with mannitol or hypertonic saline and consult neurosurgery.

37. A 64-year-old female with metastatic breast cancer presents to the ED with new back pain. The patient is ambulatory, but this week finds herself holding on to furniture or using a cane when she walks. Physical assessment reveals spinal tenderness in the L2–L3 vertebral area. X-ray findings identify osteoarthritic changes, but no other significant abnormalities. What is the next appropriate step for patient evaluation and management?
(a) Obtain CT spine
(b) Obtain MRI spine
(c) Refer to outpatient pain management services
(d) Administer zoledronic acid (zoledronate)

38. Upon review of MRI imaging, a patient is found to have a vertebral body metastasis on the T8 vertebral body. The imaging identifies a deformation of thecal sac without cord abutment. What is the grade of epidural disease based on Bilsky's grading system, and what is the likely treatment for the finding?
(a) Grade 1C; radiation therapy
(b) Grade 2; radiation therapy
(c) Grade 1B; radiation therapy
(d) Grade 1C; long-term corticosteroids

39. An 84-year-old male with prostate cancer presents with new-onset back pain, hyperreflexia, bilateral weakness in lower extremities, and urinary incontinence. The clinician has a high suspicion of metastatic spinal cord compression (MSCC), which is confirmed via MRI. Which finding provides indication of poor prognosis for this patient?
(a) Presence of MSCC
(b) Bilateral weakness in lower extremities
(c) Hyperreflexia
(d) Urinary incontinence

40. When determining medical treatment for identified metastatic spinal cord compression (MSCC), all of the following patients would be appropriate candidates for corticosteroid therapy, except:
(a) A 66-year-old male with metastatic lung cancer
(b) A 58-year-old female with metastatic breast cancer
(c) A 77-year-old male with diagnosed prostate cancer
(d) A 33-year-old male without a cancer diagnosis, presenting with back pain and scrotal edema

41. Which hormonal profile of endocrine disturbance is most common in a patient with pituitary apoplexy?
(a) Low cortisol, high prolactin, and diabetes insipidus.
(b) Low cortisol, diabetes insipidus, and other pituitary hormones normal.
(c) Low cortisol, no diabetes insipidus, and low growth hormone.
(d) Normal cortisol, diabetes mellitus, and low TSH.
(e) No hormonal disturbance is present.

42. The most common cranial neuropathy causing diplopia in patient with pituitary apoplexy is:
(a) IV nerve (trochlear nerve) palsy
(b) V nerve (trigeminal nerve) palsy
(c) IX nerve (glossopharyngeal nerve) palsy
(d) III nerve (oculomotor nerve) palsy
(e) II nerve (optic nerve) dysfunction

43. Hemorrhage within a pituitary tumor on an MRI of the sella is best conformed by the presence of which of the following features?
(a) Isointense on T1-weighted images for the first 3 days, turning hyperintense thereafter
(b) Hyperintense on T1-weighted images for the first 24 hours, turning hypointense until day 7, then turning hyperintense again
(c) Hyperintense on T2-weighted images until day 7, turning hypointense thereafter
(d) Isointense on T1-weighted images for the first 3 days, turning hypointense thereafter
(e) Hypointense on T1-weighted images both before and after gadolinium contrast is given

44. Which of the following is *not* a factor predisposing patients to develop pituitary apoplexy?
(a) Coagulopathy
(b) Hypertension
(c) Use of rivaroxaban
(d) Pregnancy
(e) Use of a dopamine antagonist

45. A 65-year-old male heavy smoker presents with 6 weeks of progressively worsening hoarseness, dysphagia, and dyspnea with a 20-pound weight loss over that period. He is seated in the tripod position and has

biphasic stridor on examination. What is the most appropriate next step in management while awaiting an otolaryngology consult?
(a) CT neck soft tissue with contrast
(b) Emergent intubation in the ED
(c) Intravenous steroids
(d) Intravenous saline bolus

46. A 74-year-old male with a history of advanced squamous cell carcinoma of the base of tongue treated with concurrent chemoradiation 6 years prior presents with acute bleeding from the mouth this morning. He had been at work when he had brisk bleeding from his mouth which resolved spontaneously after approximately 5 minutes. His vitals are within normal limits other than mild tachycardia and his hemoglobin is 8.7 g/dl. He is no longer having any active bleeding and is breathing comfortably on room air. What is the next appropriate step in management?
(a) Urgent intubation
(b) CT angiogram of head and neck
(c) GI consultation
(d) Discharge with close outpatient follow-up

47. A 62-year-old male nonsmoker presents to the ED with an enlarging right neck mass over the past few months. He has not noticed any dysphagia, odynophagia, voice changes, or dyspnea. His vital signs are normal. On CT neck, he is noted to have a 3 cm cystic mass of the right neck. What is the most likely diagnosis?
(a) Branchial cleft cyst
(b) Lymphoma
(c) Abscess
(d) Metastatic squamous cell carcinoma

48. Which of the following features on presentation is most suggestive of sinonasal malignancy rather than acute bacterial sinusitis?
(a) Bilateral nasal congestion
(b) Facial pain and pressure for 14 days
(c) Facial paresthesia
(d) Purulent nasal drainage

49. A 48-year-old female presents with lower extremity claudication several months after beginning therapy with a new medication for acute lymphocytic leukemia. Which is the most likely medication responsible for her premature peripheral artery disease?
(a) Doxorubicin
(b) Trastuzumab
(c) Ponatinib
(d) Ibrutinib

50. A 53-year-old male presents with dyspnea and chest discomfort 28 days after initiation of pembrolizumab to treat non–small cell lung cancer. Which of the following is true regarding myocarditis induced by immune checkpoint inhibitors?
(a) Troponin is always abnormal.
(b) Symptoms usually appear within the first few months of therapy.
(c) Cardiac MRI is always required for diagnosis.
(d) ECG never appears normal.

51. A 74-year-old female is hospitalized with new systolic heart failure 10 years after doxorubicin therapy for breast cancer. Which of the following options have been suggested for prevention of anthracycline-induced cardiac dysfunction?
(a) Angiotensin-converting enzyme inhibitors
(b) Beta blockers
(c) Dexrazoxane
(d) All of the above

52. A 62-year-old male is admitted with stress cardiomyopathy following infusion with 5-fluorouracil for rectal adenocarcinoma. When is stress cardiomyopathy most commonly reported to associate with chemotherapy?
(a) Initial chemotherapy infusion
(b) Last chemotherapy infusion
(c) Second chemotherapy infusion
(d) Mid-cycle chemotherapy infusion

53. A 56-year-old male with a history of non–small cell lung cancer presents with worsening shortness of breath due to a large loculated pleural effusion. He had undergone three thoracenteses recently for symptomatic recurrent pleural effusions. The last thoracentesis was aborted early due to chest pressure after draining 300 ml of pleural fluid. Pleural studies reveal lymphocytic rich exudative with negative cytology. What is the best next step?
(a) Repeat therapeutic thoracentesis.
(b) Perform pleuroscopy/medical thoracoscopy, pleural biopsy, and talc pleurodesis.
(c) Insert a chest tube and perform chemical pleurodesis.
(d) Perform pleuroscopy, pleural biopsy and insert an indwelling pleural catheter.

54. A 78-year-old female with a history of coronary artery disease, diabetes, and HFrEF of 35% underwent an AICD placement successfully and was transferred to the recovery room. While patient was in the recovery room, he developed acute onset dyspnea and left-sided chest pressure requiring supplemental oxygen. His SPO_2 was varying between 85% and 89% on 4 liters of supplemental oxygen. Stat chest X-ray at the bedside showed a moderate pneumothorax on the left side.

Patient undergoes a left chest tube placement with improvement in symptoms. Which statement is correct regarding the management of pneumothorax?

(a) Large chest tube (20–24 F) helps in resolution of pneumothorax.
(b) There is no evidence that large chest tubes (20–24 F) are better than small bore chest tubes (10–14 F) in the management of pneumothoraces.
(c) Positive pressure helps resolve pneumothoraces rapidly.
(d) Endobronchial valves have no role in the treatment of persistent air leaks from pneumothorax.

55. Which statement regarding permissive hypercapnia in patients with ARDS using low tidal volume ventilation is incorrect?
(a) Rise of $PaCo_2$ increases tissue oxygenation by right shift of oxygen–hemoglobin dissociation curve.
(b) Hypercapnic acidosis increases cyclic mechanical stretch, epithelial injury, and cell death.
(c) Hypercapnic acidosis increases epithelial injury and cell death compared to normocapnia.
(d) Hypercapnic acidosis reduces cyclic mechanical stretch, epithelial injury, and cell death.

56. A 68-year-old MALE with history of squamous cell lung carcinoma presented to ED with complains of moderate hemoptysis (30–40 cc) for the past 5 days. He remains hemodynamically stable with oxygen saturation of >95% but continues to have cough blood clots. Which of the following would be the best approach to the treatment?
(a) Nebulized tranexamic acid (TXA)
(b) Cough suppressants and supportive care
(c) Emergent surgical consultation
(d) Therapeutic bronchoscopy

57. A 34-year-old homeless female with stage IV breast cancer, undergoing doxorubicin treatment presents to the ED with a swollen right lower extremity, with erythema of the calf and foot, and exquisite tenderness to right calf. What test should be ordered, and once the diagnosis is made what would be the appropriate therapy?
(a) D-dimer, if positive, start a TSA (target specific anticoagulation) and follow-up with oncologist as scheduled.
(b) DVT ultrasound, if positive DVT, CTPA of the chest to rule out pulmonary embolism, and then initiate lovenox at 1 mg/kg to bridge to vitamin K antagonist. Ultimately discharge patient home with follow-up.
(c) DVT ultrasound, if positive for DVT, admit to the hospital for further workup and treatment.
(d) DVT ultrasound, if positive for DVT, discharge with target-specific anticoagulation (TSA).

58. A 65-year-old male with diabetes and hypertension, as well as a new diagnosis of pancreatic cancer, presents to the ED with shortness of breath. He looks ill, panicking, visibly short of breath, with a blood pressure of 85/45, heart rate of 120 beats per minute, SpO_2 of 88% on room air, SpO_2 of 94% on 6 L nasal cannula, and a temperature of 37 °C. STAT laboratory results demonstrate an elevated troponin and elevated pro-BNP, and bedside ultrasound demonstrates an enlarged right ventricle without an effusion. What is the next step in management of this patient?
(a) CTPA of the chest to confirm diagnosis of pulmonary embolism
(b) Obtain D-Dimer, if elevated, CTPA of the chest to confirm pulmonary embolism
(c) Interventional radiology consultation of direct thrombolysis
(d) Systemic fibrinolysis

59. A 66-year-old female with a history of non–small cell lung cancer is sent to the ED after being told she has a pulmonary embolism seen incidentally on a routine follow-up chest CT scan. It is a single subsegmental pulmonary embolism with no evidence of right heart strain on CT scan. She also has no leg swelling or calf pain. Her vital signs are within normal limits and she has no complaints. What is the best next step in management of this pulmonary embolism?
(a) Since it was an incidental finding, discharge without patient follow-up.
(b) Obtain basic laboratory results, initiate intravenous heparin infusion and admit to telemetry.
(c) Patient is Hestia, high risk for outpatient management. Start lovenox in the ED, so the admitting team can bridge to a vitamin K antagonist.
(d) Obtain basic laboratory results, if creatinine clearance is normal discharge on rivaroxaban and follow-up with the oncologist in 1 week.

60. A 65-year-old male with hyperlipidemia, hypertension, and a 50-pack year smoking history presents with unilateral left lower extremity swelling for 4 days. He has associated left calf tenderness, and tenderness along the left deep venous system. He had a cough a few weeks ago with some blood tinged sputum but that has resolved. His vital signs are normal, and he has obvious left lower extremity swelling and some redness. Homan's sign is positive, D-dimer is elevated,

and subsequent left leg duplex ultrasonography demonstrates partially occlusive thrombosis of the popliteal vein. A diagnosis of DVT is made. What is the best next step in this patient's care?

(a) Obtain CTPA of chest to evaluate for lung cancer, and if positive, admit to the hospital for workup of his cancer and initiation of anticoagulation.
(b) Discharge home on anticoagulation and inform the patient that he must follow up with his primary care physician to be evaluated for malignancy as well as additional other causes of VTE.
(c) First-time DVTs do not require any further evaluation; the patient can complete 3 months of anticoagulation and follow-up as needed.
(d) Obtain CTPA to evaluate for pulmonary embolism, if positive, consult interventional radiology for IVC filter and admit the patient on lovenox for bridging to vitamin K antagonist.

61. A 62-year-old man with squamous cell carcinoma of the lung presents to the ED with weakness, nausea, and shortness of breath. His cancer is stage IV, and he has had three cycles of treatment with pembrolizumab, carboplatin, and paclitaxel. He had been a long-time smoker and has chronic obstructive pulmonary disease (COPD). In the ED, he is tachypneic with a respiratory rate of 30/min. He is not hypoxic on room air by pulse oximetry. His vital signs are otherwise normal. His physical examination is normal except for signs of dehydration. What is the differential diagnosis?
(a) Diabetic ketoacidosis
(b) Pneumonia (bacterial or viral, including COVID-19)
(c) Immune pneumonitis
(d) Pulmonary embolism
(e) COPD exacerbation
(f) B, C, D, and E
(g) All of the above

62. A 65-year-old man with advanced melanoma has received 2 cycles of the combination of nivolumab and ipilimumab, and now presents to the ED with headache, general weakness (too weak to get out of bed), nausea, and loss of appetite. He was brought in by ambulance. On arrival, his vital signs are: BP 89/40 mmHg, pulse 89/minute, respiratory rate 18/minute, oxygen saturation on room air 96%, and temperature 96.5 °F. He is listless but easily arousable and is oriented to time, place, and person. Initial supportive care is initiated including intravenous normal saline bolus. His complete blood count with differential is normal, but the comprehensive metabolic panel shows a serum sodium of 128 mEq/L, chloride of 93 mEq/L, and bicarbonate of 28 mEq/L. His electrocardiogram shows no ST segment changes suggestive of myocardial ischemia. What is the next step(s) to diagnose the cause of his symptoms?
(a) Stat random cortisol level and adrenocorticotropin level
(b) TSH and free thyroxine
(c) MRI of the sella
(d) All of the above

63. A 36-year-old woman with papillary thyroid carcinoma presents to the ED with numbness and tingling of hands and feet. She was discharged home from the hospital 2 days ago after she underwent total thyroidectomy 4 days ago. She complains that her left calf is painful after she had a leg cramp when she woke up that morning. Her vital signs are normal. Her surgical wound is within normal limits of a postoperative status. No hypoxia. No chest pain. No dyspnea. No edema. What is the most likely diagnosis?
(a) Deep venous thrombosis in the left leg
(b) Anxiety attack and hyperventilation causing numbness and tingling of hands and feet
(c) Hypothyroid symptoms due to postsurgical hypothyroidism
(d) Postoperative hypoparathyroidism

64. A 55-year-old woman with metastatic colon cancer has had her 3 cycles of chemotherapy with panitumumab, 5-fluorouracil, and oxaliplatin 4 days ago. She presents to the ED for general weakness and muscle cramping. She is irritable and has been crying. Her CBC-diff showed mildly depressed blood counts that do not require transfusion. Her complete metabolic panel shows sodium 133 mEq/L, potassium 3.3 mEq/L, calcium 8.0 mg/dL, and magnesium 0.3 mg/dL. Which of the following statement is true?
(a) Stat EKG, and monitor cardiac rhythm while electrolyte abnormalities are corrected with intravenous infusions since the patient is at high risk for cardiac arrhythmia.
(b) Hypomagnesemia causes PR shortening and thereby increases the risk for torsade de pointes.
(c) Hypomagnesemia is caused by the nephrotoxic effect of oxaliplatin and is unrelated to 5-fluorouracil and panitumumab.
(d) All of the above are true.

65. One of the following is the least effective endoscopic hemostatic modalities for GI bleeding related to tumors:
(a) Cryotherapy
(b) Argon plasma coagulation
(c) Nd-YAG laser

(d) Endoscopic clips
(e) Hemostatic powders (when available on the market)

66. In patients who need palliation of their symptoms due to duodenal obstruction from pancreatic cancer, an enteral stent should be placed if their life expectancy is expected to be greater than 6–12 months.
(a) True
(b) False

67. All of the following are potential causes of fulminant hepatic failure in a patient with cancer, except:
(a) Chemotherapy
(b) Innumerable hepatic metastases
(c) Total parenteral nutrition
(d) Malignant infiltration of the liver with lymphoma or adenocarcinoma
(e) Polypharmacy/drug-induced liver injury

68. Which of the following is *not* an indication for ERCP for biliary decompression?
(a) Intolerable pruritus
(b) Intolerable jaundice
(c) Acute cholangitis
(d) Abnormal LFTs without symptoms
(e) Hyperbilirubinemia that interferes with chemotherapy dosing

69. Current management of adhesive small bowel obstruction includes nonoperative management for up to 3 days, as long as the patient does not deteriorate with symptoms suggesting intestinal ischemia.
(a) True
(b) False

70. Advanced malignant disease in the upper gastrointestinal tract can result in gastric outlet obstruction. The most common malignant cause of gastric outlet obstruction is:
(a) Pancreatic cancer
(b) Periampullary cancer
(c) Advanced gastric cancer
(d) Duodenal and jejunal cancer

71. The classic presentation of neutropenic enterocolitis is a patient with absolute neutrophil count <1000 cells/μL, new-onset abdominal pain, and fever. Most commonly it occurs:
(a) 1 week after receiving cytotoxic chemotherapy
(b) 2–3 weeks after receiving cytotoxic chemotherapy
(c) 4 weeks after receiving cytotoxic chemotherapy

72. Acute radiation enteritis usually occurs between 2 and 6 weeks postradiation therapy. Clinical manifestations include nausea, vomiting, abdominal pain, and diarrhea associated with blood and mucus. Possible complications include:
(a) Systemic sepsis
(b) Gastrointestinal bleeding
(c) Bowel obstruction
(d) All of the above

73. A 30-year-old woman with colon cancer and Lynch syndrome. She had metastatic colon cancer that has started to progress after first-line cytotoxic chemotherapy. She has just received the third cycle of ipilimumab and nivolumab 3 days ago. She presents to the ED with severe watery diarrhea. She had more than 8 bowel movements in the past 24 hours. Her blood pressure is normal, but she is tachycardic. Her bowel sound is hyperactive. Her right upper quadrant tenderness is unchanged. Which of the following are true?
(a) The patient may have grade 3 immune-mediated colitis, and CT scan of the abdomen and pelvis is indicated.
(b) Call the gastroenterology consult team to arrange for colonoscopy and biopsy.
(c) Collect stool samples for culture and various other tests for infectious diarrhea (including *C. difficile* toxins).
(d) All of the above.

74. A 65-year-old patient with advanced VIPoma currently on long-acting pegylated octreotide now presents to the ED with worsening of chronic diarrhea. Over the last week, his stool frequency gradually increased to 6 times per day. He feels weak and dehydrated. Which of the following is true?
(a) This is a chronic problem, and the patient can be discharged from the ED after intravenous hydration with isotonic crystalloid solutions and replacement of electrolytes.
(b) Intravenous octreotide is not helpful since the patient is already on long-acting octreotide injections.
(c) Consult interventional radiology to evaluate whether reduction of tumor burden by chemoembolization is possible.
(d) None of the above.

75. A 55-year-old man with acute myeloid leukemia, who had allogeneic hematopoietic stem cell transplant 3 weeks ago, presents to the ED with severe diarrhea, nausea, and vomiting for 2 days. He has had 10 watery large volume bowel movements in the past 24 hours despite taking loperamide around the clock. What is the appropriate management if he is hypotensive, tachycardic, and hypokalemic?

(a) Obtain blood cultures, urine culture, and urinalysis; initiate intravenous fluids 30 mL/kg; and start broad-spectrum empirical antibiotics.
(b) Collect stool sample for *C. difficile* toxin assay, multiplex PCR for gastrointestinal pathogens, and stool culture.
(c) Discuss with the stem cell transplant team to consider starting intravenous glucocorticoid therapy.
(d) All of the above.

76. A 22-year-old woman with acute lymphoblastic leukemia, s/p 2 cycles of hyper-CVAD chemotherapy presents to the ED for sudden onset fever, chills, and mild epigastric abdominal pain. She had a CBC-diff the day before, and her absolute neutrophil count was 100 per microliter. She reports that she has had 2 watery bowel movements in the past 8 hours. Which is the following is true?
(a) CT scan of the abdomen and pelvis is indicated to diagnose neutropenic enteritis.
(b) Prescribe a lidocaine containing gastrointestinal cocktail to control esophageal and gastric pain from chemotherapy, and loperamide for mild chemotherapy-induced diarrhea. No further investigation of the gastrointestinal tract is needed.
(c) Initiate intravenous cefepime for neutropenic fever in the ED, prescribe loperamide for the mild diarrhea, and discharge the patient on home intravenous antibiotic therapy.
(d) None of the above.

77. A 56-year-old woman with glioblastoma multiforme presents to the ED with complains of not having a bowel movement for over 4 days. She has had intermittent constipation in the past and this feels similar. She also complains of nausea. Her vital signs are normal and her examination is unremarkable, except for mild dehydration. What is the best next step in management?
(a) Give her ondansetron for her nausea and hydrate her with intravenous fluids.
(b) Give her metoclopramide for her nausea and hydrate her with intravenous fluids.
(c) Obtain a plain radiograph to evaluate for bowel obstruction and stool burden, and hydrate her with intravenous fluids.
(d) Hydrate her with intravenous fluids.

78. A 22-year-old woman with breast cancer with metastasis to the bone presents to the ED with constipation of over 1-week duration. She has a history of chronic constipation since being diagnosed with metastatic bony disease. She is on a chronic opioid regimen. She recently increased the dose of her opioid due to uncontrolled cancer pain. After a thorough workup, including a digital rectal examination, you conclude that she has uncomplicated, likely opioid-induced constipation. What is the best next step in management?
(a) Give the patient methylnaltrexone.
(b) Give the patient senna and bisacodyl.
(c) Encourage the patient to eat more fiber.
(d) Disimpact the patient in the ED.

79. An 80-year-old male with metastatic prostate cancer to the bone presents to the ED with constipation. He has not had a bowel movement for over 1 week and is complaining of lower back pain, which he attributes to the constipation. The review of systems reveals tingling of the lower extremities. A thorough physical examination reveals mild weakness of lower extremities and bony tenderness over the spine but otherwise normal. What is the best next step in management?
(a) Give the patient analgesics and start IV fluid hydration, while you await laboratory results.
(b) Give the patient a milk and molasses enema.
(c) Order an emergent MRI of the spine to evaluate for malignant spinal cord compression or conus syndrome.
(d) Order and emergent CT of the abdomen to evaluate for intra-abdominal pathology.

80. A 62-year-old male presents with constipation for over 2 weeks. On arrival to the ED, he is noted to have a temperature of 38 °C (100.4 °C), a heart rate of 140 beats per minute, and blood pressure of 100/60 mmHg. He complains of diffuse abdominal pain and nausea. On physical examination, he is ill appearing and has a diffusely tender abdomen with distention and rebound tenderness. What is the most important next step in managing this patient?
(a) Obtain a CBC, chemistries, and a CT of the abdomen with contrast.
(b) Send a sepsis workup, including lactic acid.
(c) Give the patient an IV fluid bolus and obtain a stat upright portable chest radiograph.
(d) Call a surgical consult.

81. All of the following drugs are associated with thrombotic microangiopathy (TMA), except:
(a) Cisplatin
(b) Gemcitabine
(c) Anti-VEGF therapy
(d) Ifosfamide

82. All of the following are effective therapies for methotrexate (MTX) toxicity, except:
(a) IV hydration to increase urine output
(b) Bicarbonate to increase solubility of MTX in the urine

(c) Dialysis to clear MTX
(d) Glucarpidase to metabolize MTX into inactive compounds

83. All of the following may be used in the treatment of SIADH, except:
(a) Normal saline
(b) Salt tablets
(c) Vasopressin receptor antagonists
(d) Fluid restriction

84. Which one of the following is true about tumor lysis syndrome?
(a) Rasburicase may be used in the treatment of established TLS to decrease serum uric acid levels.
(b) Allopurinol will help to breakdown uric acid in the bloodstream.
(c) Preemptive dialysis is an established treatment for the prevention of TLS.
(d) Routine alkalization of the urine is part of the treatment of established TLS.

85. A 63-year-old man underwent radical prostatectomy 1 week ago. His Foley catheter was removed 36 hours ago. He initially voided well, but experienced hematuria and a weak stream after a bout of coughing. He now presents to the ED complaining of lower abdominal pain and an inability to void for 10 hours. After initial evaluation, the ED provider should:
(a) Proceed with an urgent CT scan of the abdomen and pelvis.
(b) Place a 22-French Foley and irrigate the bladder until clear.
(c) Place an 18-French Foley and initiate continuous bladder irrigation.
(d) Contact the urology service, immediately.

86. Continuous bladder irrigation (CBI) is indicated in the patient with persistent gross hematuria:
(a) If the patient passes large clots
(b) When there is difficulty irrigating clots from the bladder
(c) Once all sizeable clots have been evacuated from the bladder
(d) After anticoagulation has been discontinued

87. In a patient with ureteral obstruction and infection, the factor that triggers decompression of the urinary system with retrograde ureteral stenting versus percutaneous nephrostomy tube placement is the:
(a) Active use of anticoagulants
(b) Service line availability
(c) Etiology of the obstruction
(d) All of the above

88. A 75-year-old woman underwent right partial nephrectomy for a 3 cm renal carcinoma. One week later she presents to the ED with gross hematuria and right flank pain. She is hemodynamically stable with a normal WBC, creatinine, and a hemoglobin of 11 g/dl. The next step is to:
(a) Discharge home with follow-up within 1 week.
(b) Monitor the patient in the ICU.
(c) Proceed with a CT angiogram.
(d) Obtain a CT urogram and urine cytology.

89. A 68-year-old female recently diagnosed with metastatic ovarian cancer was found to be confused with muscle weakness and diminished reflexes. Which laboratory abnormality would be the cause of the symptoms?
(a) Hypocalcemia
(b) Hypercalcemia
(c) Hyperchloremia
(d) Hypochloremia

90. A 45-year-old female who has been undergoing carboplatin and paclitaxel for ovarian cancer presents with a temperature of 38.0 °C for at least an hour. What other laboratory abnormality would you need to diagnose febrile neutropenia?
(a) ANC $\leq$ 500 cells/mm^3
(b) ANC $\geq$ 500 cells/mm^3
(c) ANC $\leq$ 300 cells/mm^3
(d) ANC $\leq$ 400 cells/mm^3

91. Which of the following is *not* a noninvasive method for control of bleeding in a patient with advanced cervical cancer?
(a) Palliative radiotherapy
(b) Vaginal packing
(c) Percutaneous uterine artery embolization
(d) Volume replacement

92. A 58-year-old patient with a history of ovarian cancer treated with intraperitoneal cisplatin and paclitaxel presents to the ED with vomiting, constipation, abdominal distension, and abdominal pain. CT scan shows bowel thickening and mesenteric stranding. The patient's temperature is within normal limits. What would be the most likely diagnosis?
(a) Diverticulitis
(b) Intestinal obstruction
(c) Chemotherapy-induced enterocolitis
(d) Pelvic inflammatory disease

93. A 72-year-old female with history of hypertension and a 30-pack year smoking history presents with left leg pain and inability to ambulate. She has had pain in her

mid-left tibia for the past 4 weeks and while walking to the restroom this morning, felt a pop with associated deformity. On physical examination, her left leg is grossly deformed, but the skin is intact. Her compartments are soft without associated numbness or tingling, and distal pulses remain palpable. Radiographs show a large lytic lesion in the tibial diaphysis with a displaced pathologic fracture. What is the most likely diagnosis, and how should additional workup in the ED proceed?

(a) Primary bone sarcoma. CT of the chest, abdomen, and pelvis with laboratory workup assessing for myeloma and primary sarcoma. Leg should be immobilized in a short leg splint.
(b) Primary bone sarcoma. CT of the chest, abdomen, and pelvis with laboratory workup assessing for myeloma and primary sarcoma. Leg should be immobilized in a long leg splint.
(c) Metastatic disease. CT of the chest, abdomen, and pelvis with laboratory workup assessing for myeloma and metastatic disease. Leg should be immobilized in a short leg splint.
(d) Metastatic disease. CT of the chest, abdomen, and pelvis with laboratory workup assessing for myeloma and metastatic disease. Leg should be immobilized in a long leg splint.

94. A 65-year-old male with history of metastatic prostate cancer to the left femoral neck, 8 weeks status post left total hip replacement, presents to the ED with inability to bear weight. He was standing up after using the toilet earlier this morning and felt a sudden pop in his left hip. He is neurovascularly intact. Laboratory results are not concerning for infection. What are radiographs likely to show? What is the most likely position of his leg on physical exam? What is the most appropriate management in the ED?

(a) Posterior dislocation of left total hip replacement. Shortened, flexed, adducted, internally rotated. Conscious sedation and closed reduction
(b) Anterior dislocation of left total hip replacement. Shortened, flexed, abducted, externally rotated. Conscious sedation and closed reduction
(c) Vancouver B periprosthetic fracture. Shortened, slightly externally rotated. Buck's traction
(d) Vancouver C periprosthetic fracture. Shortened, slightly externally rotated. Buck's traction

95. A 48-year-old female with history of diabetes and soft-tissue sarcoma in her left lateral thigh, who received preoperative radiation and is now 3 weeks status post radical resection, presents to the ED with her son, who status she "doesn't seem like herself." On examination, she has marked erythema and induration about her surgical incision with multiple hemorrhagic bullae. There is a focal area of wound dehiscence distally with "dishwater" fluid draining. She is oriented to person, but not place or time. She has a WBC of 34,000/mm^3, hemoglobin of 9.8 g/dL, sodium of 128 mmol/L, and CRP of 320 mg/L. CT does not show any evidence of gas. What is the most likely diagnosis and what is the most appropriate next step?

(a) Cellulitis. Empirical antibiotics and potentially surgery
(b) Abscess. Admission to the hospital and surgery within the next 24–48 hours
(c) Necrotizing fasciitis. Emergent surgical consult and surgery
(d) Suture reaction. Oral antibiotics and discharge home

96. A 68-year-old male with acute myelogenous leukemia on chemotherapy presents with acute onset pain and swelling in his right leg. Pain started earlier this morning. He states he may have bumped his leg on the dresser, but he does not recall any significant trauma. Pain has continued to increase throughout the day and has been unresponsive to oral analgesia. He is alert and oriented. He has marked swelling about his leg. He has decreased sensation on the dorsum of his foot. Peripheral pulses remain palpable. Pain is exacerbated anteriorly by passive plantar flexion of his great toe. The leg is firm and incompressible. He has WBC of 1600/mm^3, hemoglobin of 7.3 g/dL, and platelet count of 8000/mm^3. Radiographs are unremarkable. What is the most likely diagnosis and what additional tests are necessary prior to any definitive intervention?

(a) Pathologic fracture. CT scan should be obtained to better clarify the fracture.
(b) Compartment syndrome. No additional studies are needed.
(c) Abscess. MRI should be performed to both confirm diagnosis and assess for additional pathologic findings.
(d) Compartment syndrome. A manometer (i.e., Stryker needle) should be used in all four compartments of the leg to confirm diagnosis prior to surgery.

97. DRESS/DIHS (drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome) is most commonly characterized by which of the following?

(a) Skin pain, skin blistering, targetoid lesions, fever
(b) Maculopapular rash, facial edema, fever, eosinophilia
(c) Urticaria and angioedema
(d) Pustules, fever, neutrophilia

98. Which of these statements regarding immune-related cutaneous adverse events (ircAEs) to immunotherapy is false?
    (a) The most common manifestations are pruritus and maculopapular rash.
    (b) They can be distinguished from cutaneous adverse drug reactions to regular medications by skin biopsy.
    (c) They may be associated with prolonged progression-free survival and overall survival.
    (d) They can occur at any time during or even after treatment.
99. Which of the following skin morphologies can reflect cutaneous blood vessel lumen occlusion (i.e., thrombosis/embolic)?
    (a) Macular purpura
    (b) Palpable purpura
    (c) Ecchymoses
    (d) Retiform purpura
100. Which of the following is *not* a criterion of SCORTEN severity illness score for predicting mortality in SJS/TEN?
    (a) Number of mucosal sites involved
    (b) Heart rate >120
    (c) Age >40
    (d) Initial percentage of epidermal detachment >10%
101. A 4-year-old girl undergoing chemotherapy for acute lymphoblastic leukemia and is known to be neutropenic presents with new onset abdominal pain and tenderness in the right lower quadrant on physical examination. A rare but potentially fatal complication of pretreatment is diagnosed on ultrasound. The findings on ultrasound that would support this include:
    (a) A "target sign" found in the right lower quadrant
    (b) A blind ended bowel loop with a noncompressible hyperemic bowel wall
    (c) A cystic structure in the periumbilical region
    (d) A thickened bowel wall located in the right lower quadrant
    (e) A "whirlpool sign" in the right lower quadrant
102. A patient who recently started chemotherapy for Burkitt's lymphoma with high tumor burden is being monitored for complications of therapy. Laboratory testing of the blood would be expected to show:
    (a) Low potassium
    (b) Low calcium
    (c) Low phosphorus
    (d) Low urea nitrogen
    (e) Low sodium
103. As pediatric oncologic patient survival rates increase due to advances in medications and treatment protocols, delayed mortality is most notably due to:
    (a) Sepsis
    (b) Suicide
    (c) Arrhythmias
    (d) Interstitial lung disease
104. Pediatric cancers present in many ways, typically with vague complaints. Which of the following is not a typical presentation seen?
    (a) Fatigue
    (b) Weight gain
    (c) Bone pain
    (d) Fever
    (e) Pallor
105. A 69-year-old man is in the ED with worsening shortness of breath. His wife also states that he appears more confused lately and has not had an appetite in the last couple of days. His white blood sound count is 120,000/mm^3 with 93% blasts. He has a history of acute myeloid leukemia with plans to start treatment in the next few days. On physical examination, the patient is only oriented to self, oxygen saturation is 92% on room air, heart rate is 113, but afebrile. Chest radiographs indicate bilateral infiltrates, but no focal lesions or consolidations, pneumothorax, or pleural effusion. Oncologic was consulted and will see the patient. Meanwhile, what is the initial management in the ED?
    (a) Antibiotics
    (b) Hydroxyurea
    (c) Isotonic intravenous fluids
    (d) Leukapheresis
106. A 75-year-old woman with a history of ALL is brought to the ED by her family for "acting funny." Her daughter reports that her mother has seemed more confused over the past few days, and now is not using her right hand to feed herself. On physical examination, vital signs are all within normal limits. The patient is disoriented and has right-sided weakness. CBC is notable for WBC 60,000/mm^3, platelet count 6000/mm^3, and hemoglobin 6.5 g/dL. Which of the following is the best initial diagnostic test to obtain?
    (a) CT head without contrast
    (b) MRI brain
    (c) Lumbar puncture
    (d) EEG
107. A 39-year-old man without major past medical history is sent in from the local urgent care for abnormal laboratory work. He reports feeling run down and fatigued with a decreased appetite and nonproductive cough for the past few weeks, and thought he maybe had the flu. His vital signs are notable for a heart rate of 128 and a respiratory rate of 30 but are otherwise within normal limits. He appears pale, dry, and tachypneic with mild retractions, but denies shortness of breath. His paper-

work from urgent care shows a WBC count of 205,000/mm^3, hemoglobin of 7 g/dL, platelets of 18,000/mm^3, creatinine of 3 mg/dL, a bicarbonate of 12 mmEq/L, a lactate of 4 mmol/L, troponin of 1.9 ng/mL, and a venous blood gas with a pH of 7.25 and a PCO_2 of 27 cmH_2O. His EKG shows sinus tachycardia with lateral ST segment depressions. You start IV fluids and send a page to the on-call oncologist immediately. What is the best way to manage this patient while waiting for the oncologist to return your page?

(a) Give aspirin 324 mg and start a heparin drip
(b) Transfuse packed red blood cells to a goal hemoglobin of 8–10 mg/dL
(c) Administer empiric antibiotics
(d) Intubate

108. A 56-year-old man with history of hypertension and chronic back pain presents with a triage complaint of "back pain." He is moaning a lot and not providing a lot of answers to your questions. His family reports that they knew something was wrong when he did not go to his methadone clinic today. Vital signs: temperature 37.3 °C (99.1 °F), heart rate 104 beats per minute, blood pressure 156/93, respiratory rate 27 breaths per minute, oxygen saturation 94% on room air. You obtain lab work that demonstrates a WBC count of 87,000/mm^3, hemoglobin of 5.9 g/dL, platelets of 9000/mm^3, potassium of 5.6 mmol/L, CO_2 of 15 mmol/L, a creatinine of 2.7 mg/dL, a calcium of 7.6 mg/dL, and a phosphorus of 6 mg/dL. His chest X-ray is clear, and his lumbar spine X-ray is consistent with degenerative joint disease. You consult the on-call oncologist who asks for a manual differential, uric acid, LDH, coagulation studies, initiation of intravenous fluids, and admission to the hospitalist. What is the appropriate next step in this patient's care?
    (a) Initiate sodium bicarbonate infusion
    (b) Obtain a noncontrasted CT scan of the head
    (c) Transfuse 2 units of packed red blood cells and 1 pack of platelets
    (d) Administer IV calcium
109. For patient with cancer and acquired factor VIII inhibitors, eradication of the tumor is crucial to controlling the inhibitor.
    (a) True
    (b) False
110. Which one of these antineoplastic therapies has been associated with low antithrombin levels?
    (a) Bevacizumab
    (b) Hydroxyurea
    (c) L-Asparaginase
    (d) Thalidomide
111. Which mutation is associated with thrombosis in myeloproliferative neoplasms?
    (a) BCR-ABL
    (b) CALR
    (c) JAK2
    (d) MPL
112. A rare cause of bleeding in patients with myeloproliferative neoplasms is acquired deficiency of factor:
    (a) V
    (b) VII
    (c) X
    (d) XI
113. A 19-year-old woman with a history of sickle cell disease presents with pain in her legs. She says it is her typical pain crisis and denies shortness of breath, chest pain, or nausea. Laboratory testing reveals the following: WBC count, 10,000/mcL; Hgb, 4 g/dL; and reticulocyte count, 0.5%. Electrolytes are normal. She responds well to pain medication. Which of the following treatments is helpful for her condition?
    (a) Antibiotic therapy
    (b) Exchange transfusion
    (c) Oxygen administration
    (d) Transfusion of packed red blood cells
114. A 24-year-old man presents to the ED after 1 week of worsening left shoulder pain. He has had pain over the past 2 months intermittently. He denies any fever, trauma, swelling, or rash. He has a history of sickle cell disease. His vital signs are normal. You order an X-ray of the left shoulder. What finding is likely to be demonstrated on the X-ray?
    (a) Avascular necrosis
    (b) Fracture of the humerus
    (c) Osteomyelitis
    (d) Tumor in the lung
115. A 19-year-old male presents to the ED 1 week after his last visit complaining of pain in his legs that is typical of his symptoms on prior visits. When should laboratory tests including a CBC, reticulocyte count, LFTs, bilirubin, LDH, and electrolytes be considered?
    (a) The patient is being admitted.
    (b) You suspect another diagnosis.
    (c) The patient appears toxic.
    (d) All of the above.
116. A 38-year-old woman with a known history of sickle cell disease comes into the ED 1 week after her last uneventful pain crisis. She complains of 3 days of nonproductive cough and gradual onset severe central chest pain radiating to both shoulders. She admits to being short of breath on exertion. Her vitals show a temperature of 38.2 °C, heart rate of 108/min, blood

pressure of 126/78 mmHg, and an oxygen saturation of 92% on room air. She is short of breath on examination and her lung sounds are clear. She has a normal cardiovascular exam. A chest X-ray is ordered. Which of the following chest radiograph findings is likely to be present?
(a) Multilobar infiltrates
(b) Pneumothorax
(c) No acute pathology
(d) Rib fracture

117. A 19-year-old man presents to the ED with acute change in mental status. Over the past 3 weeks, he has been experiencing progressive fatigue, easy bruising, and new bleeding from his gums. In the days prior to admission, he developed headache in the left periorbital area and recently complained to his family of double vision. His physical examination is concerning for an obtunded patient who is responsive to questions but incoherent. He has esotropia of the left eye. Initial laboratory results demonstrate anemia, thrombocytopenia, and an elevated white count that is predominantly lymphocytic. His other leukocyte lineages are suppressed, including neutrophils, with an absolute neutrophil count of 400 cells per μL. CT head demonstrates acute inflammation of the left nasal sinus and associated periorbital fat stranding with a radiologist impression of acute invasive fungal sinusitis. Which of the following is the best next step?
(a) Order STAT MRI
(b) Start liposomal amphotericin B
(c) Start micafungin
(d) Order NP swab for culture

118. A 62-year-old woman with metastatic cholangiocarcinoma currently receiving gemcitabine plus cisplatin presents to the ED for fever and abdominal pain. Her second cycle of chemotherapy was given in the outpatient cancer infusion center via her port approximately 1 week ago. On initial evaluation, she is febrile but alert and stable. She notes severe right lower abdominal pain which comes in waves. She states for several days she has noted diarrhea; however, today it became maroon in color before stopping. Initial laboratory work demonstrates a hemoglobin of Hgb 9.2 mg/dL, a platelet count of 112,000 per μL, and an ANC of 250 cells per μL. She is started on empiric cefepime and metronidazole. Which of the following is the best next step?
(a) CT scan of the abdomen
(b) Add IV vancomycin to the empiric antibiotics
(c) Give colony-stimulating factor for neutropenia
(d) Send stool C difficile toxin assay

119. A 65-year-old woman with metastatic breast cancer receiving chemotherapy presents to the ED with fever, chills, and night sweats. She has a tunneled internal jugular central venous catheter in place through which she has been receiving chemotherapy as well as intravenous fluids and total parenteral nutrition per home nursing due to dehydration and poor oral intake. Vital signs are notable for an oral temperature of 38.4 °C, BP 100/60 mmHg, and HR 72 bpm. She appears chronically ill but is in no acute distress. The insertion site for the catheter is notable for mild erythema but no induration or drainage. There is no tenderness to palpation along the subcutaneous tract of the catheter. Which of the following is the best next step?
(a) Start empiric IV vancomycin and cefepime
(b) Draw 2 sets of blood cultures from the central venous catheter
(c) Obtain 2 sets of blood cultures from separate peripheral venous sites
(d) Coordinate immediate removal of the central venous catheter

120. A 54-year-old man with a history of hematopoietic stem cell transplant (HSCT) 6 months ago presents with worsening cough and dyspnea on exertion over the past 3 weeks. His HSCT has been complicated by graft-versus-host disease, requiring chronic immunosuppression including high-dose corticosteroids. The patient is currently taking valganciclovir and fluconazole; he was also supposed to be taking trimethoprim-sulfamethoxazole, but this was held approximately 2 months back due to acute kidney injury. In triage, he is notably hypoxic with the pulse oximeter reading 86% on room air. A chest radiographic demonstrates diffuse ground glass opacities. With which of the following opportunistic infections is this patient's clinical presentation most consistent?
(a) CMV pneumonia
(b) HSV pneumonia
(c) *Pseudomonas aeruginosa* pneumonia
(d) *Pneumocystis jirovecii* pneumonia

121. A 16-year-old male with leukemia presents to the ED with a temperature of 38.5 °C and a mild, dry cough. His vital signs are otherwise within normal limits, and his laboratory results are unremarkable. His fever resolves without treatment and he feels otherwise well. In addition to initiating antibiotic therapy, what is the next step in this patient's care?
(a) Apply the MASCC score to risk stratify the patient
(b) Apply the CISNE score to risk stratify the patient

(c) Place the patient in observation status
(d) Admit the patient for ongoing antibiotics and close monitoring

122. A 43-year-old female with a history of osteosarcoma presents to the ED with a temperature of 39 °C. It has been approximately 7 days since her last chemotherapy and she is found to be neutropenic. She reports using a mask and gloves at all times and is wondering how she developed this infection. What is the most likely source?
(a) She likely has a noninfectious cause such as drug or tumor fever.
(b) She probably contracted her infection from her kids.
(c) She most likely developed the infection from endogenous flora.
(d) She likely became infected during her last infusion center visit.

123. The following are considered safe discharge criteria for patients with febrile neutropenia except:
(a) Residence ≤4 hours or ≤100 miles (160 km) from clinic or hospital
(b) Access to a telephone and transportation 24 h/d
(c) Family member or caregiver at home 24 h/d
(d) No history of noncompliance with treatment protocols

124. A patient with leukemia has been diagnosed with low-risk febrile neutropenia is cleared for discharge, but he is very concerned that he will not be receiving intravenous antibiotics. What does the evidence say regarding the use of oral versus intravenous antibiotics in febrile neutropenia?
(a) Oral antibiotics are inferior to intravenous antibiotics in all cases.
(b) Oral antibiotics and intravenous antibiotics are equally effective.
(c) Oral antibiotics are noninferior to intravenous antibiotics in cases of low-risk febrile neutropenia.
(d) Oral antibiotics are never indicated in patients with hematologic malignancies.

125. A 70-year-old man with acute myeloid leukemia presents to the ED after suddenly developing fever, diffuse abdominal pain, and diarrhea. You are very concerned for neutropenic enterocolitis and consult the hematology/oncologic and surgical teams. Based on the above presentation, your diagnostic approach should include:
(a) Immediate surgical consultation and transfer to the operating room for bowel resection.
(b) Evaluation for GVHD and *C. diff* as well as CT imaging to help characterize the diagnosis.
(c) Bedside ultrasound to make a definitive diagnosis followed by administration of antibiotics and admission.
(d) Immediate administration of broad-spectrum antibiotics and ICU admission, CT imaging is unnecessary at this time.

126. A 70-year-old man with acute myeloid leukemia presents to the ED after suddenly developing fever, diffuse abdominal pain, and diarrhea. On physical examination, he has right lower quadrant abdominal pain with associated guarding and bowel sounds are present. Laboratory evaluation reveals a white blood cell count of 1200 cells/μL (ANC = 100/dl), a hematocrit of 23%, and 40,000 platelets/μL. Computed tomography (CT) scan of the abdomen and pelvis shows thickening of the colonic wall with diffuse pericolic edema and pneumatosis. What additional information will help guide a decision regarding surgery?
(a) Extent of bowel wall thickening
(b) Persistent GI bleeding
(c) Involvement of the cecum
(d) Chemotherapeutic regimen

127. Risk factors for neutropenic enterocolitis in the above patient include all of the following, except:
(a) Specific chemotherapeutic agent
(b) Timing from last chemotherapy
(c) Route of administration of chemotherapy
(d) Tumor type (i.e., solid vs. hematogenous)

128. Blood cultures and stool studies for *Clostridium difficile* and other enteropathogenic organism are pending for the above patient. Besides broad-spectrum antibiotics and close hemodynamic monitoring, what additional therapies might the patient benefit from?
(a) Recombinant granulocyte colony-stimulating factor (G-CSF)
(b) Corticosteroid
(c) Rasburicase
(d) Recombinant factor VIIa

129. What are the three domains of biopsychosocial model?
(a) Hypothalamus–pituitary–adrenal axis
(b) Predisposing, precipitating, and perpetuating factors
(c) Childhood trauma, anger, and impulsive behavior
(d) Environmental, financial, and psychosocial factors

130. Cancer patients have a higher risk for suicide as compared to general population, because:
(a) Cancer is common in older frail people.
(b) They have financial crisis due to cancer treatment.
(c) They lose their job due to the disease.
(d) In addition to general risk factors of suicide, they have the burden of adverse effects of cancer treatment.

131. How do you differentiate depression from side effects of cancer treatment?
(a) Hopelessness and loss of interest in previously enjoyable activities

(b) Poor sleep
(c) Fatigue
(d) Weight loss

132. What would you do as the first step when discharging a low-risk suicidal patient?
(a) Give a prescription of antidepressant
(b) Arrange a follow-up with a therapist
(c) Making sure patient has no access to weapons
(d) Giving him a suicide hot line number

133. All the following information about delirium in in the cancer patient present are correct, except:
(a) Delirium is different from altered mental status.
(b) May be interpreted as worsening pain.
(c) Most delirium cases in ED are of the agitated (hyperactive) type.
(d) It is frequently missed by ED providers.

134. What are the most common causes of delirium in the cancer patient presenting to ED:
(a) Brain metastasis
(b) Liver failure
(c) Renal failure
(d) Side effects of medications
(e) Paraneoplastic syndrome

135. What is the most important step in the management of the cancer patient with delirium in the ED?
(a) Give benzodiazepine intravenously.
(b) Intubate the patient.
(c) Give any of the atypical antipsychotic medications such as olanzapine.
(d) Assure safety of the patient.
(e) Give haloperidol.

136. Which of the following statements about palliative sedation is correct?
(a) Haloperidol is commonly used for this procedure.
(b) Refractory delirium is the most common indication for this procedure among cancer patients.
(c) When stated, it should be continued until the patient die.
(d) May be started if the patient (or family) wishes to shorten life.

137. Transalar herniation can lead to infarction in which territories?
(a) Anterior cerebral artery (ACA)
(b) Middle cerebral artery (MCA)
(c) Posterior cerebral artery (PCA)
(d) A and B
(e) A, B, and C

138. What is the most common cause of massive hemoptysis worldwide?
(a) Bronchogenic carcinoma
(b) Trauma
(c) Postoperative complication
(d) Pulmonary fibrosis
(e) Pulmonary tuberculosis (TB)

139. What is the approximate attenuation in Hounsfield units (HU) of acute blood products on CT?
(a) −1000
(b) −100
(c) 0
(d) 40
(e) 1000

140. At least what percent of bone mineral density must be lost in order for radiographs to detect lytic lesions?
(a) 10%
(b) 30%
(c) 50%
(d) 70%
(e) 90%

141. A 48-year-old female with history of ovarian cancer presents with lethargy. Her husband who accompanies her notes that she was scheduled for a chemotherapy infusion today in clinic but she was "too sick to go through with it." Her vital signs: temperature 101.2 °F (38.4 °C), pulse 112 bpm, respirations 24 bpm, blood pressure 88/50, and pulse oximetry 98% on room air. She looks chronically ill, was lethargic but awake and spontaneously breathing, and was unable to provide much history. The abdomen appears distended and is generally tender to palpation. An IV is placed, a Foley is inserted with clear urine returned, and fingerstick glucose is 120. You perform a bedside ultrasound that shows the following finding on the left side only (Fig. 1). In addition to obtaining blood cultures, administering broad-spectrum antibiotics and 30 ml/kg of crystalloid fluids, what action should you take?

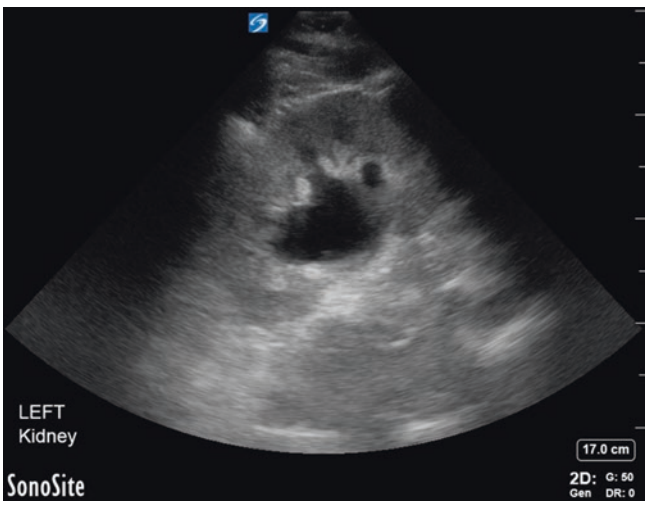

Fig. 1 Ultrasound findings

(a) Initiate dobutamine, and hold the fluids with concern for cardiogenic shock.
(b) Consult a urologist to request an emergent nephrostomy.
(c) Consult a general surgeon to request an emergent laparotomy.
(d) Consult a vascular surgeon for catheter-directed thrombolysis.
(e) Place an NG tube, make the patient NPO, and obtain a CT abdomen-pelvis to evaluate for a bowel obstruction.

142. A 22-year-old male with a history of metastatic testicular cancer presents with chest pain that began approximately 3 hours ago when he woke up. It is sharp, worse with lying flat, and partially relieved with sitting up, associated with shortness of breath and dizziness. Vital signs: temperature 98.7 °F (37.0 °C), pulse 104 bpm, respirations 20 bpm, blood pressure 103/76 by automatic cuff, and oxygen saturation 97% on room air. ECG shows sinus rhythm, rate of 104, normal axis, mild (<1 mm) ST segment elevation in all the precordial leads without depressions, and no TW inversions. The patient is thin, awake, alert, and oriented, with no obvious abnormality on cardiopulmonary examination. Bedside echocardiography reveals the following finding (Fig. 2). Which of the following management options should be considered?
(a) Catheter-directed thrombolysis
(b) Cardiac catheterization
(c) Placement of a left-sided pigtail catheter for tension pneumothorax
(d) Left thoracentesis
(e) Pericardiocentesis

143. A 39-year-old female with history of breast cancer who is currently undergoing chemotherapy presents to the ED with leg swelling for 1 week. Her vital signs were only remarkable for sinus tachycardia of 108 bpm. Upon examination, you find 3+ edema on the right lower extremity up to the mid-thigh. There is significant right calf and thigh tenderness with overlying erythema. Which of the following would confirm the suspected diagnosis?
(a) A noncompressible common femoral artery
(b) A noncompressible common femoral vein with an echogenicity in the lumen
(c) A compressible common femoral vein with the presence of luminal flow
(d) A compressible popliteal artery with luminal echogenicity

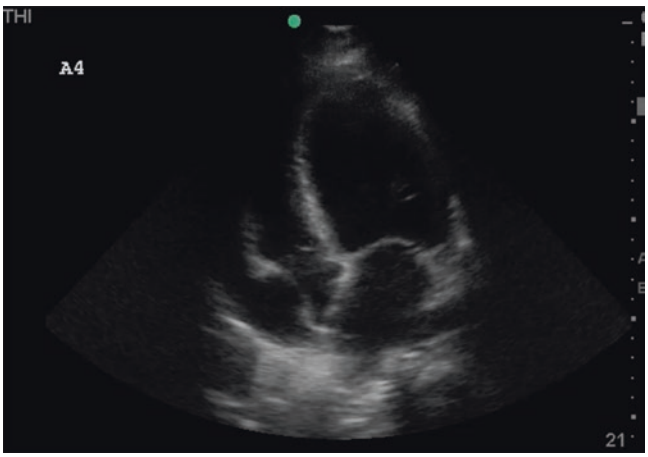

Fig. 2 Ultrasound findings

144. A 50-year-old female with breast cancer presents with shortness of breath and dyspnea on exertion. She is currently receiving doxorubicin as a chemotherapeutic agent. She has not previously had symptoms like this. Examination is remarkable for hypoxia to 90% on room air, jugular venous distension (JVD) and symmetric bilateral lower extremity edema, and obvious orthopnea. Which of these findings would confirm the suspected diagnosis?
(a) Diffuse B lines and bilateral pleural effusions on POCUS lung examination and a decreased left ventricular ejection fraction on cardiac ultrasound.
(b) Diffuse A lines on POCUS lung examination and a normal left ventricular ejection fraction on cardiac ultrasound.
(c) Diffuse A lines on POCUS lung examination and a hyperdynamic left ventricular ejection fraction on cardiac ultrasound.
(d) Significant free fluid in the abdomen on RUSH examination and a dilated IVC.
(e) Focal B lines and unilateral pleural effusion on POCUS examination of the right lung and a normal left ventricular ejection fraction on cardiac ultrasound.

145. A 50-year-old African-American female with breast cancer is receiving paclitaxel as part of her chemotherapy regimen. On a follow-up visit, she complains of symmetrical paresthesias in her legs which began in her toes a few weeks ago. She has tried over the counter pain medications with no relief. Her past medical history is significant for diabetes for which she takes metformin. She takes no other medications at this time. Which is the best evidenced-based treatment option?
(a) Gabapentin 300 mg po every 8 hours
(b) Duloxetine 30 mg po daily for 1 week then increase to 60 mg po daily
(c) Baclofen 10 mg, amitriptyline 40 mg, and ketamine 20 mg in pluronic gel apply to affected area three times daily
(d) Acupuncture

146. A 42-year-old male presents to the ED following extravasation of vincristine. The needle has been removed prior to presentation to the ED and the area of extravasation is red, swollen, and painful to touch. At this time, there is no ulceration and the affected area appears to not be progressing. Which of the following is the appropriate management for this patient?
    (a) Administer hyaluronidase to areas of extravasation
    (b) Do not elevate arm
    (c) Apply cold compress
    (d) Consult plastic surgery to evaluate the area
147. What is the most important agent for management of a patient with anaphylaxis secondary to cisplatin?
    (a) Epinephrine IM 0.5 mg into the deltoid muscle
    (b) Diphenhydramine 50 mg IV
    (c) Epinephrine IM 0.01 mg/kg IM into lateral aspect of thigh (max dose 0.5 mg)
    (d) Hydrocortisone 50 mg IV
148. A 34-year-old female who received her first cycle of fluorouracil, methotrexate, and cyclophosphamide as part of her chemotherapy regimen for breast cancer. The following day she presents to the ED with complaints of severe fatigue and confusion. Her husband states she was in her normal state of health until she woke up this morning with acute confusion. Her vital signs are normal with the exception of a slighted elevated blood pressure at 185/93 mmHg. Her home medications include sertraline 50 mg orally daily for depression and tramadol 50 mg orally as needed for pain. She has no other significant past medical history. A noncontrast CT scan of the brain in the ED is unremarkable. A recent MRI from 1 week ago showed no brain metastasis. What is the most likely cause of the patient's confusion?
    (a) Undiagnosed brain metastasis
    (b) Severe SIADH resulting in hyponatremia
    (c) Infection
    (d) Head trauma
149. Radiation treatment to the heart is associated with injury to:
    (a) Valves
    (b) Myocardium
    (c) Coronary arteries
    (d) All of the above
150. Radiation injury to the heart is influenced by:
    (a) Radiation dose
    (b) Volume in the therapy field
    (c) Daily fraction size
    (d) All of the above
151. Radiation injury to the lung can occur outside the radiation treatment field.
    (a) True
    (b) False
152. Radiation injury to the kidney generally spares the glomeruli.
    (a) True
    (b) False
153. With medical support, the LD 50/30 for total body radiation exposure is generally thought to be 5 cGy.
    (a) True
    (b) False
154. Lymphocytes may serve as a surrogate biomarker for radiation dose during an acute exposure incident.
    (a) True
    (b) False
155. Bone marrow transplant is a proven treatment for acute radiation exposure.
    (a) True
    (b) False
156. At least what percentage of pediatric patients undergoing hematopoietic stem cell transplant will experience oral and/or gastrointestinal mucositis?
    (a) 25%
    (b) 45%
    (c) 65%
    (d) 85%
    (e) 95%
157. Which of the following costs has *most contributed* to the economic burden related to oral and gastrointestinal mucositis?
    (a) Administration of antimucositis agents
    (b) Invasive procedures implemented for diagnosis of mucositis
    (c) Extended inpatient hospitalizations related to potential sequelae of mucositis
    (d) Additional time spent by physicians and clinical staff managing patient symptoms of mucositis
    (e) Enteral feeding tube intervention
158. Which of the following agents is appropriate for the prophylaxis of oral mucositis in a patient undergoing chemoradiation therapy for cancer of the head and neck?
    (a) Benzydamine mouthwash
    (b) Oral antibiotics
    (c) Hyperbaric oxygen therapy
    (d) Prebiotic supplementation
    (e) Fat-modified diet
159. Which of the following statements is true regarding mucositis?
    (a) Patient-reported duration and severity of mucositis are typically shorter and less severe compared to that reported by physicians.
    (b) Endoscopic evaluation is preferred for the diagnosis of gastrointestinal mucositis.
    (c) Early intervention with intravenous fluid hydration and/or enteral feeding tube placement is critical in

patients experiencing rapid, continuous weight loss and can reduce the risk of hospitalization or treatment break.
(d) Geriatric patients are at low risk of developing oral and gastrointestinal mucositis.
(e) Bacterial flora present in the oral and gastrointestinal mucosae have no impact on the pathogenesis of mucositis.

160. A 54-year-old male with a history of an allogeneic HCT 6 months ago for acute myeloid leukemia presents to the ED with profound melena. Vital signs showed a BP of 90/60, HR of 120, RR 18, and T 36.8 °C. CBC showed Hgb of 6 g/dL, Hct of 19%, WBC of 9.3/uL, and platelets of 150,000/uL. You decide to transfuse packed red blood cells.
(a) Washed RBC
(b) Genotypically matched RBC
(c) Leukoreduced RBC
(d) Irradiated RBC
(e) Both C and D

161. A 64-year-old man with AL amyloidosis who is undergoing autologous stem cell mobilization with high-dose G-CSF presents to the ED with lightheadedness and severe abdominal pain. Which of the following complications of high-dose G-CSF do you suspect?
(a) Pancreatitis
(b) Esophageal rupture
(c) Splenic rupture
(d) Mesenteric ischemia

162. A 52-year-old man with B-cell acute lymphoblastic leukemia receives nonmyeloablative conditioning followed by growth factor-mobilized blood cell transplantation from an HLA-matched unrelated donor. GVHD prophylaxis consists of cyclosporine, sirolimus, and mycophenolate mofetil. Twenty-one days after transplant, the patient develops new anorexia, early satiety, nausea, and low-volume diarrhea (approximately 300 mL/day). Despite scheduled antiemetics and diet adjustment, his GI symptoms persist. The patient has lost 5.0 kg over 1 week. The patient and donor were both CMV seropositive. Which of the following represents the best approach to treating this patient?
(a) Discontinue mycophenolate mofetil as this is the most likely cause of GI symptoms.
(b) Treat empirically with ganciclovir for presumed CMV enteritis.
(c) Refer to gastroenterology for consideration of endoscopic studies to evaluate for acute GVHD and test for viral infection.
(d) Treat empirically with prednisone at 2.0 mg/kg/day.

163. A 22-year-old patient with peripheral T-cell lymphoma presents to the ED with language incoherence noticed by his wife and gait change of 12-hour duration. The patient feels well and states he feels it is normal since he recently underwent CD19-chimeric antigen receptor (CAR)-T-cell therapy.
(a) Calculate the immune effector cell-associated encephalopathy (ICE) score since the symptoms can be a delayed presentation of immune effector cell-associated neurotoxicity syndrome (ICANS).
(b) Call the stroke team.
(c) Refer the patient to neurology clinic.
(d) Discharge the patient without further evaluation since the patient feels normal.

164. A 65-year-old patient with advanced melanoma has received 3 cycles of the combination of nivolumab and ipilimumab, and now presents to the ED with chest pain. He has no risk factors or family history of coronary artery disease. His electrocardiogram shows no ST segment changes suggestive of myocardial ischemia or pericarditis. What is the best next step in management?
(a) Discharge the patient if normal initial troponin level.
(b) Obtain D-dimer and 3 sets of cardiac enzymes. Initiate aspirin and anticoagulation (if no brain metastasis). Rule out myocarditis from immune checkpoint inhibitors.
(c) Start the patient on dexamethasone.
(d) None of the above.

165. A patient with acute myeloid leukemia presents to the ED with fever, hypotension, renal failure, and transaminitis. What is the appropriate management if the patient presents a card stating he is on oral therapy with enasidenib, which was started 3 weeks ago?
(a) Draw cultures, initiate intravenous fluids 30 mL/kg, and start broad-spectrum antibiotics.
(b) Admit to the intensive care unit.
(c) Consider the diagnosis of differentiation syndrome and initiate dexamethasone therapy after discussion with the oncologist.
(d) All of the above.

166. A patient with acute lymphoblastic leukemia presents to the ED for sudden onset fever, chills, and shortness of breath about 15 minutes upon reaching home after receiving blinatumomab infusion in the ambulatory treatment center. What is the best next step in management?
(a) Assess the patient's airway for vital signs and respiratory status and administer oxygen support.
(b) Evaluate for acute infection, probable neutropenic fever, and empirically start broad-spectrum antibiotics.

(c) Treat with corticosteroid, antihistamines, and inhaled beta-agonists for a delayed infusion reaction syndrome or cytokine release syndrome.
(d) All of the above.

167. What is one of the key indicators of poor quality care with regard to ED visits at the EOL?
(a) More than 2 visits in the last 6 months of life
(b) Avoidable visits in the last year of life
(c) More than 1 ED visit in the last 30 days of life
(d) Less than 1 ED visit in the last 6 months of life

168. What is the benchmark population value rate that regions should strive to be below for patients with cancer accessing ED care?
(a) 50%
(b) 80%
(c) 10%
(d) 30%

169. Which of the following is not among the 3 most common reasons for ED visits for patients with cancer at end of life?
(a) Fever
(b) Pain
(c) Shortness of breath
(d) Nausea

170. Research has shown that receipt of palliative care services is associated with various outcomes. Which of the following is not one of them?
(a) Better symptom control
(b) Improved knowledge of expectations
(c) Shorter survival
(d) Decreased chemotherapy use

171. Patients can develop tolerance to which adverse effect of opioids?
(a) Respiratory depression
(b) Constipation
(c) Pruritus
(d) All of the above

172. Which of the following statements is true about neuropathic pain?
(a) Peritoneal carcinomatosis generally causes neuropathic pain.
(b) Anticonvulsants require close titration of dosing when treating neuropathic pain.
(c) Topical lidocaine patches should be worn continuously for maximum treatment of neuropathic pain.
(d) Corticosteroids are contraindicated in neuropathic pain.

173. Which opioid does not follow first-order kinetics?
(a) Morphine
(b) Dilaudid
(c) Methadone
(d) Fentanyl

174. A 40-year-old woman presents to the ED in severe pain that she rates as 8/10. Her only past medical history is breast cancer. Twenty minutes after receiving a dose of IV morphine, she has no adverse side effects of the morphine but her pain remains 8/10. What is the best next step for her pain control?
(a) Repeat the same dose of IV morphine at this time.
(b) Re-assess the patient in 30 minutes because the first dose has not had sufficient time to work.
(c) Increase the initial dose by 50–100% and administer a second IV dose at this time.
(d) Switch to intramuscular morphine for more reliable absorption.

175. A 61-year-old man with a history of metastatic prostate cancer currently receiving radiation presents to the ED complaining of constipation. He is taking morphine daily for pain control but does not take medications to prevent constipation. After ruling out stool impaction and bowel obstruction, you discuss the case with the patient's oncologist and determine the patient is safe for discharge. You plan to send him home with a prescription to ease his constipation? Which of the following is true regarding medications for opioid-induced constipation prophylaxis?
(a) Methylnaltrexone is considered the best first-line agent for opioid-induced constipation prophylaxis.
(b) Stimulants and osmotic agents are often used together.
(c) Stimulants act by increasing water content in the large bowel.
(d) Polyethylene glycol is considered a bulk-forming agent.

176. The risk factors for a substance abuse problem developing in a person being treated for cancer pain with opioids include all of the following except:
(a) Older age
(b) Male gender
(c) Personal psychiatric history
(d) Family history of substance abuse

177. Pseudo addiction refers to a syndrome in which a person in poorly controlled pain develops aberrant behaviors that are uncharacteristic of them under normal circumstances and are expected to resolve when adequate pain control is provided. Which of the following are true of pseudo addiction:
(a) Pseudo addiction is mutually exclusive from actual loss of control of one's medications and the development of drug abuse.
(b) The behaviors always resolve with the provision of improved analgesia alone.
(c) It is best thought of as similar to secondary alcoholism.

(d) The original concept came from a large clinical trial.

178. In a study examining documentation of alcohol problems in 100 alcoholics with advanced illness, how many had their alcohol history noted in their medical record?
(a) 80%
(b) 60%
(c) 55%
(d) 30%

179. Disulfiram (Antabuse) has been shown to work in some highly selected patients with alcoholism. Which of the following characteristics does not predict the likelihood of a response to Antabuse?
(a) Older than 40 years of age
(b) Shorter drinking histories
(c) Socially stable
(d) Highly motivated

180. A 70-year-old patient with advanced lung cancer, enrolled in hospice care, presents to the ED with severe shortness of breath. The patient's goals are to focus on comfort and quality of life and to stay at home, but his caregiver panicked and called 911 when his breathing worsened. On physical examination, the patient reports severe dyspnea and appears very uncomfortable with a RR of 35 with accessory muscle use. The most important next step is to:
(a) Intubate the patient
(b) Place the patient on BIPAP
(c) Administer a test dose of morphine 2 mg IV and reassess for symptomatic improvement
(d) Get a STAT chest X-ray

181. In patients with advanced cancer presenting in respiratory distress, noninvasive ventilation
(a) Should always be used as a first step
(b) May be beneficial to some and can be utilized if consistent with the patient's goals of care
(c) Is rarely helpful and should not be considered
(d) Leads to recovery with discharge to home in nearly all patients

182. Diagnoses that commonly lead to dyspnea in patients with advanced cancer include:
(a) Pleural effusions
(b) Anemia
(c) Tumor burden in lungs
(d) All of the above

183. A 60-year-old patient with advanced pancreatic cancer is brought in by EMS after being found down in her home. She was with her friend at the time of the event. EMS arrived and found the patient in cardiac arrest, with an initial rhythm of PEA. ACLS protocol was initiated, the patient was intubated, and eventually ROSC was achieved. The patient's spouse has now arrived in the ED and says that the patient was DNR/DNI and did not want to be kept alive on machines at this stage of her illness. The most appropriate next step would be to:
(a) Walk into the room and remove the ETT.
(b) Counsel the patient's spouse that extubation is not allowed.
(c) Provide emotional support to the patient's spouse, counsel him on the patient's expected prognosis off the ventilator, and then start gathering the appropriate medications for extubation.
(d) Explain that extubations are only possible in the ICU.

184. Which of the following statements is true regarding outcomes treatments in cancer patients?
(a) Most patients with stage IV lung cancer understand that chemotherapy will cure their cancer.
(b) Less than 5% of hospitalized older patients with end-stage cancer knew that the CPR success rates were <10%.
(c) Physicians tend to rate more end-of-life items as significantly more important than patients.
(d) More than 60% of seriously ill older adults consider inability to "get out of bed" as a better quality of life than death.

185. Which of the following statements is *not* true regarding healthcare professional's concerns about family-witnessed resuscitation?
(a) Some hospitals may have inadequate resuscitation space per patient volume.
(b) Family-witnessed resuscitation causes additional stress to healthcare workers and thus negatively impacts their performance.
(c) Family members are not expected to understand the procedures and may interfere resuscitation efforts.
(d) Presence of family members may increase the potential for litigation in the future.
(e) The family members generally understand that resuscitation does not always result in positive outcome.

186. What is the most likely precipitating cause of in-hospital CPR in cancer patients?
(a) Anaphylactic reaction
(b) Respiratory failure
(c) Arrhythmia
(d) Cardiac arrest
(e) Hypovolemia

187. Which of the following conditions may have a worse outcome if a patient with such condition were to require CPR?
(a) Lymphoma

(b) Breast cancer
(c) Colorectal cancer
(d) Genitourinary cancer
(e) Head and neck cancer

188. Which of the following are considered by experts to be essential components of goals-of-care conversations in the ED?
(a) Identify the minimum quality of life the patient is willing to live for.
(b) Identify the surrogate decision maker if patient lacks capacity.
(c) Respond to emotion to reduce the anxiety/stress from discussing goals of care.
(d) Make a recommendation based on patient's baseline function, minimum quality of life acceptable, and prognostic estimates.
(e) Understand the baseline physical function and quality of life of the patient.
(f) All of above.

189. When should palliative care be started?
(a) Patients planning for tumor resections and starting chemotherapy
(b) Actively dying patients in ED
(c) Patients with chronic life-limiting illnesses such as congestive heart failure or chronic obstructive pulmonary disease
(d) When all cancer treatments have stopped
(e) A and C

190. Who would be the most effective ED palliative care champion?
(a) Medical students
(b) Quality control personnel
(c) Spiritual care personnel
(d) Hospital legal representatives
(e) ED volunteers

191. A 77-year-old man with advanced dementia, lung cancer with metastases to brain, presents from a nursing facility with increasing shortness of breath. He is bedbound and dependent on nursing care. There is a do not resuscitate/do not intubate order on his chart. His current vital signs are BP, 90/54; P, 105; R, 28; and T, 101.0 °F. Oxygen saturation is 89% on 4 L O_2 by nasal cannula. What is the most appropriate next step for patient management?
(a) Referral to in-patient hospice
(b) Intubation and admission to ICU
(c) Oxygen, antibiotics, and consult palliative care team
(d) Bereavement counseling
(e) Admit to hospitalist team for comfort care

192. In which scenario should an urgent consult to palliative care consult team be of most benefit in the ED?
(a) A patient with severe malignant bowel obstruction who refuses surgical intervention
(b) A patient with severe back pain and suspected acute cord compression
(c) A new diagnosis of multiple metastases from a breast malignancy
(d) A patient with severe vomiting after chemotherapy for lung cancer

193. In which scenario should hospice services referral be appropriately considered in the ED?
(a) A patient with dementia and prostate cancer
(b) Elderly patient with multiple myeloma and fall at home with hip fracture
(c) A patient with a chronic lymphocytic leukemia and a large left middle cerebral artery cerebrovascular accident or stroke
(d) Homeless patient with alcohol dependence and liver cirrhosis with a lung mass
(e) Any patient where expected survival is 6 months or less

194. A 43-year-old female has had evidence of worsening pain with known history of metastatic breast cancer to brain, lung, and bones. She has undergone radiation therapy as well as received steroids to manage her symptoms. You find that after repeated bolus IV doses of opioid analgesia, her pain remains uncontrolled and initiate a PCA. Her nurse tells you that she has improved; however, that she has been in the room frequently offering support and reassessing her symptoms. After clarifying goals of care, she has elected hospice with her family and her goal is to just get the pain under control. What level of hospice care does she likely require?
(a) Home hospice
(b) Facility-based care
(c) Continuous hospice care
(d) Inpatient unit care

195. A 75-year-old male has had progression of known prostate cancer and no longer has further traditional treatment options available per discussion with his oncologist after he presents to you with worsening back pain. After further discussion, he wants to pursue hospice, but remembers that there is a medication that has worked to provide longer life for patients in his situation and is off-label. He asks you if this medication will be covered by hospice?
(a) Yes, this medication is covered.
(b) No, it is not covered; it is a treatment that is meant to treat his underlying terminal condition.
(c) Call his oncologist to discuss.
(d) Look up the medication yourself to determine if it is effective or not.

196. A 50-year-old woman with a past medical history significant for recent diagnosis of metastatic pancreatic cancer not considered amenable to surgical intervention. She has experienced a rapid decline in clinical status, including obstructive jaundice, and due to this as well as complicating comorbidities of lupus with need for systemic immunosuppression, she was not considered a candidate for further therapies. She elected hospice and presents to the ED from home with bilious emesis. Further evaluation reveals likely SBO mechanical obstruction and she is not a candidate for surgical intervention. Her symptoms are temporized by a nasogastric tube (NGT), and she wishes to return home in lieu of admission but has severe ongoing nausea. What level of hospice is likely best able to control her symptoms at this point?
    (a) She can return home; the hospice IDT should be able to manage her symptoms there.
    (b) Continuous care should be able to transition her to home from the hospital.
    (c) Respite care is the best option because her husband does not know how to manage a nasogastric tube.
    (d) Inpatient unit care is most appropriate given her severe ongoing symptoms for stabilization prior to returning home.
197. Which of the following can emergency clinicians always rely on for appropriate guidance when faced with ethical dilemmas?
    (a) Institutional and medical board policies
    (b) The American College of Emergency Physicians' (ACEP) Code of Ethics
    (c) The American Medical Association or American Osteopathic Association ethical statements
    (d) None of the above
198. What are "values"?
    (a) The standards that individuals, institutions, professions, and societies use to judge human behavior.
    (b) The correct way of thinking about issues.
    (c) A patient's normal view of medicine, society, and his or her family.
    (d) A sense of duty to patients required of all healthcare workers.
199. Withholding treatment in the ED:
    (a) Legally differs from withdrawing treatment.
    (b) Morally differs from withdrawing treatment.
    (c) Requires clinical information that is often unavailable immediately.
    (d) Should never be done.
200. When using the "rapid approach to ethical problems" in the ED to decide on a course of action:
    (a) Always consult with the bioethics committee/consultant before acting.
    (b) Assume that each ethical problem in the ED requires a unique solution.
    (c) Test your chosen action against your religious values.
    (d) When practicable and safe for the patient, buy time to consult on possible options.
201. Which one of the following statements is false?
    (a) Members of the LGBTQ community can be more difficult to research due to lack of standard collection of sexual orientation and gender identity in the health record.
    (b) Members of the LGBTQ community are less likely to live in poverty and more likely to have health insurance.
    (c) Sexual orientation relates to identity rather than sexual behavior.
    (d) Lack of employment discrimination protection is common, and in many states, you can be fired for being gay or transgender.
202. The minority stress model
    (a) Only applies to racial and ethnic minorities
    (b) Has not been shown to contribute to cancer disparities in minority groups
    (c) Does not apply if all patients are treated equally
    (d) Is thought to explain the negative effects of chronic stigmatization and high levels of stress on a minority group's health status
203. Cancers are with worse outcomes in the black community include:
    (a) Colon cancer
    (b) Breast cancer
    (c) Lung cancer
    (d) All of the above
204. Which of the following is not true?
    (a) Minority populations will overtake the majority white population by 2050.
    (b) Cultural humility is a lifelong process of self-reflection and self-critique that can inform understanding of cultural differences and how differences require sensitive approaches to healthcare.
    (c) Outright discrimination is also known as implicit bias.
    (d) Minority groups are often underrepresented in cancer clinical trials.
205. Which of the following is true regarding bias:
    (a) Biases are shaped by experiences and based on learned associations between particular qualities and social categories.
    (b) Raising awareness of physician bias and how they affect clinical decision-making is key to helping physicians mitigate bias.
    (c) Patients with schizophrenia and other disabilities are often unable to advocate for themselves and

are also at increased risk of experiencing physician bias.
(d) All of the above.

206. Choose the correct statement about WHO analgesic ladder:
(a) Provides a simple approach toward treating pain in only 50% of the patients.
(b) The first step of the ladder represents the use of nonopioid and opioids analgesics to treat mild pain.
(c) The second step represents the use of weak opioids with or without nonopioid analgesics, and with or without adjuvants to treat moderate pain.
(d) States to administer pain medications on-demand instead of around-the-clock.
(e) Intravenous and rectal dosing of drugs is preferred whenever possible.

207. Cancer pain can be characterized as:
(a) Neuropathic pain
(b) Somatic (nociceptive) pain
(c) Sympathetic pain
(d) A and C
(e) All of the above

208. Choose the correct statement about methadone:
(a) Rapid titration is safe.
(b) Withdrawal symptoms are more severe than morphine.
(c) Sedation and respiratory depression can outlast the analgesic action.
(d) Never used in opioid addiction.
(e) Lacks interactions with multiple medications that the patients may be on.

209. Which of the following is true regarding tramadol?
(a) Has a dose limit of 800 mg/d
(b) No effect on norepinephrine or serotonin
(c) Inhibits the reuptake of norepinephrine and serotonin
(d) Is a peripherally acting analgesic
(e) Has strong opioid characteristics

210. The specialties of emergency medicine and oncologic are organizing to establish professional groups to organize activities around oncologic emergency medicine, including educational, research, and policy initiatives. Which groups below are representative of these efforts?
(a) American Academy of Emergency Medicine Oncologic Emergency Medicine Interest Group
(b) Society for Academic Emergency Medicine Oncologic Emergencies Interest Group
(c) American College of Emergency Physicians Oncologic Emergency Medicine Section
(d) NIH-supported Comprehensive Oncologic Emergencies Research Network (CONCERN)
(e) B and D
(f) A and C

211. Of the options below, which factors pose barriers to establishing quality metrics for oncologic emergency medicine?
(a) Gaps in existing ED measures
(b) Fragmented measure development
(c) Difficulty defining the episode of oncologic emergency care
(d) Measurement without a clear mechanism for improving ED care
(e) Challenges in obtaining ED quality data
(f) All of the above

212. The first patient navigator program was:
(a) Developed by the Dana Farber Cancer Center in 2005
(b) Developed by The University of Texas Cancer Center in 1994
(c) Developed by Harlem Hospital in 1990
(d) Developed by the Intermountain Healthcare system in 2002

213. In what year was Emergency Nursing established as a specialty practice by the American Nurses Association?
(a) 1970
(b) 1986
(c) 1992
(d) 2011

214. In addition to the acute medical needs that prompt ED visits and invite the interventions of ED social workers, oncologic social workers serve to address the unique psychosocial stressors that accompany a cancer diagnosis. These may include:
(a) Adjustment to a new cancer diagnosis
(b) Alterations in role and identity
(c) Changes in caregiver needs and family roles
(d) Impact on work and finances
(e) Goals of care planning
(f) All of the above

215. All of the following statements regarding radiation are true, except:
(a) Radiation is the passage of an electromagnetic wave through space.
(b) Nonionizing radiation includes radio waves, microwaves, and ultrasound.
(c) X-rays and gamma rays are examples of ionizing radiation.
(d) Gamma rays are produced when electrons are emitted from electron clouds as a result of electron excitation.

(e) Radiation is considered ionizing if it is of high enough energy to remove electrons from an atom.

216. Which of the following statements regarding lung cancer screening is true?
   (a) Gays, lesbians, and bisexuals have higher rates of smoking, thus higher levels of lung cancer screening than their heterosexual counterparts.
   (b) Geographically in the United States, the South has 40% of lung cancer screening-eligible patients and a screening rate that is one-third that of the Northeast.
   (c) The NCI-funded National Lung Screening Trial (NLST) failed to demonstrate mortality reduction with lung cancer screening.
   (d) The 1986 Mayo Lung Project found a benefit in overall mortality for subjects receiving lung cancer screening.
217. The most common tumor causing proptosis in adults is:
   (a) Optic nerve glioma
   (b) Lymphoma
   (c) Orbital rhabdomyosarcoma
   (d) Meningioma
218. Superior vena cava syndrome (SVCS) represents one of the most common oncologic emergencies seen in the ED.
   (a) True
   (b) False
219. All of the following regarding radioactivity are true, except:
   (a) One Sievert (Sy) is equivalent to 1000 roentgen equivalent man (rem).
   (b) One gray (Gy) is equivalent to 1 J of energy deposited in 1 kg of tissue.
   (c) Radioactivity is measured in curies (Ci) in the English measurement system.
   (d) Radioactivity is measured in Becquerel (Bq) in the SI system.
   (e) A Becquerel (Bq) is equivalent to one disintegration of an atomic nucleus per second.
220. Which of the following are true statements?
   (a) The antidote for fluoropyrimidine toxicity is oral capecitabine.
   (b) Treatment of 5-FU toxicity is largely supportive.
   (c) 5-Fluorouracil is the oral prodrug of capecitabine.
   (d) Hand-and-foot syndrome is a characteristic adverse effect of uridine triacetate.
   (e) Uridine triacetate toxicity is generally attributed to genetic polymorphisms.

Answers

1. (b) Over 60% of patient with pancreas, brain, and lung cancer have at least one ED visit within 1 year of diagnosis. Overall, 44% of all cancer patients have one ED visit within 1 year of diagnosis. Less than 30% of those with melanoma, prostate, eye, or endocrine cancers have a visit within 1 year of diagnosis.
2. (a) Approximately 4% of all ED visits are cancer-related, and lung, breast, prostate, and colon are the most frequent cancers associated with ED visits.
3. (d) Visit-level data only provide information about patients who visit the ED and do not capture all patients with cancer. While visit-level data may provide valuable information regarding the quality, type of care, and related diagnosis, visit-level data are unlikely account for multiple visits made by the same patient.
4. (e) Current methodologies generally utilize ICD codes and diagnoses to identify potentially avoidable ED visits; however, no common consensus definition exists to define which diagnoses or visits made by cancer patients are preventable.
5. (c) While specific visit and admission rates vary by cancer type, oncologic patients have higher rates of admission from the ED and higher rates of multiple ED visits than the general US population.
6. (e) HIPAA defined 18 potential identifiers. Of the above choices, gender is the least likely to uniquely identify a patient and does not meet these definitions.
7. (c) A cancer registry is an information system that collects and analyzes data from a census of cancer cases. Registry data can be used to define and monitor cancer incidence, investigate treatment patterns, evaluate efforts to prevent cancer, and improve survival.
8. (e) Polling providers for preference, along with scouring the literature for recommendations and guidelines, are often first steps in designing an order set. Usually, one or more clinical "champions" are identified to begin the process of consulting literature, guidelines, experts in the domain, and practitioners in the affected departments.
9. (a) A current smoker is someone who has smoked at least 100 cigarettes lifetime and currently smokes every or some days.
10. (d) The patient is experiencing nicotine withdrawal after several hours of not smoking. She would benefit from nicotine replacement therapy. Combination treatments that include a short-acting medication (nicotine gum) supplemented by a long-acting medication (nicotine patch) are often more efficacious in treating nicotine withdrawal than patch alone.
11. (b) Both nicotine replacement therapy and motivational interviewing are efficacious. Tobacco control, in general, is among the most cost-effective treatments in all of medicine. National bodies do not mandate tobacco treatment in the ED, although the Model of the Clinical Practice of Emergency Medicine does require EM residents be taught the principles of tobacco dependence treatment.
12. (c) SBIRT does require smokers to be referred for post-ED treatment of tobacco dependence. Although tobacco pharmacotherapy may begin in the ED, SBIRT does not require it. Adding nicotine replacement to SBIRT is consistent with the newer treatment model known as Screening, Treatment Initiation, and Referral (STIR). SBIRT was initially developed to treat individuals with alcohol-use disorders, then adapted to tobacco and other substances. There are no contraindications to delivering SBIRT, although patients should of course be able to engage in a meaningful conversation with the interventionist.
13. (a) Alcohol use most commonly begins during adolescence. As youth transition into late adolescence, alcohol use typically increases.
14. (c) Evidence supports a dose-dependent relationship between alcohol use and cancers of the breast, rectum, and larynx. Uterine cancer is not known to be closely linked to alcohol use.
15. (d) Native American populations have the highest rates of alcohol-attributable injuries such as MVCs and falls compared to other racial/ethnic minority groups. Black and Latino populations have the highest rates of recurrent or persistent alcohol dependence, once it has developed. Among all racial/ethnic minority groups, Asians populations have the lowest reported rates of alcohol use.

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16. (b) The DSM-5 removed the category of alcohol-related legal problems, which was present in the DSM-IV, and replaced it with the criteria of craving. Both tolerance and withdrawal were previous criteria for alcohol dependence in the DSM-IV. They are also criteria for alcohol-use disorder in the DSM-5.
17. (b) Total excision. All the other options may be useful for smaller lesions where total removal with the technique may be possible in depth and width, but risk base transection occurring or sampling error where the segment sampled of a lesion does not give an accurate reflection of its true nature (mild dysplasia abutting in situ melanoma in the same lesion). If uncertain regarding diagnosis or management, dermatology or teledermatology referral can be an alternative solution.
18. (c) The presence of a darker skin type on the Fitzpatrick scale is less likely to develop melanoma.
19. (b) Increasing Breslow thickness correlates strongly and negatively with 10-year survival.
20. (a) "A" in the ABCDE patient mnemonic stands for asymmetry, not aggravating.
21. (d) It is unclear if protection is life-long, but it is at least 10 years. Because the vaccines do not provide protection against all cancer-associated HPV types, routine cervical screening is still recommended, including routine screening in vaccinated women.
22. (c) Guidelines recommend screening for cervical cancer between the ages of 21 and 65. Cervical cancer screening should not be performed in women younger than 21 years of age, regardless of the age of onset of sexual activity. From ages 30–65, cervical cytology and HPV testing are recommended.
23. (c) Observation is preferred to treatment for women with CIN 1. In general, women with CIN2/3 are treated because of the higher risk of progression to invasive cancer. Treatment to remove abnormal areas of the cervix may be through ablation (with cryotherapy or thermal ablation) or excision of the precancerous area. Excisional procedures include loop electrosurgical excision procedure (LEEP), cold knife conization (CKC), and CO_2 laser conization. In the United States, excisional treatment is preferred to ablative treatment.
24. (d) Approximately 80% of individuals with HPV will clear the infection spontaneously within 18–24 months of infection. In women with persistent HPV infection, 3–5% will develop significant preinvasive disease, and <1% will develop cancer.
25. (d) This patient presents with a likely bowel obstruction from colon cancer. Important considerations include his history of ulcerative colitis and lack of subsequent follow-up. Long-standing ulcerative colitis is associated with a significant increased risk of colon cancer and regular screening for dysplasia is recommended. Toxic megacolon may also present with systemic toxicity and colon dilation. Bloody diarrhea and distension are seen throughout the entire colon without a point of transition. Acute diverticulitis may have a systemic toxic presentation but distension is unlikely. While underlying ulcerative colitis is strongly associated with primary sclerosing cholangitis and ascending cholangitis, bowel obstruction is unlikely and a cholestatic pattern is seen with liver function tests.
26. (c) Occult fecal bleeding and hematochezia do not necessarily indicate the presence of advanced colon malignancy, and they are found in some individuals with early colorectal cancer.
27. (d) The patient has symptoms worrisome for colon carcinoma and will need a definitive diagnosis to guide therapy. CT colonography is a useful diagnostic method; however, the risk of radiation and need for further studies, such as colonoscopy, should be considered. Colonoscopy is the most accurate diagnostic method, can localize and provide a definitive tissue diagnosis, and can remove polyps.
28. (b) Upright abdominal series to look for free air. The patient has a history of colon cancer and suddenly developed abdominal pain suggestive of a bowel perforation. If she is unable to tolerate an abdominal series, a CT of the abdomen and pelvis would be the next step.
29. (d) Stabilization of a patient with hemoptysis and respiratory distress begins with establishing a protected airway in the form of endotracheal intubation. Once intubated, further steps to identify and isolate, such as with an endobronchial blocker or selective mainstem intubation, can be performed.
30. (c) Patients with greater dyspnea and poorer functional status derived the most benefit from therapeutic bronchoscopy based on data published from the AQuIRE registry. (Ost DE, Ernst A, Grosu HB, et al. Therapeutic bronchoscopy for malignant central airway obstruction: Success rates and impact on dyspnea and quality of life. *Chest*. 2015;147(5):1282–1298.)
31. (c) Patency of the lobar bronchi distal to the obstruction. Patency of distal airways, either on CT or on bronchoscopy, has been identified as predictors of a successful therapeutic bronchoscopy to relieve MCAO. (Ost DE, Ernst A, Grosu HB, et al. Therapeutic bronchoscopy for malignant central airway obstruction: Success rates and impact on dyspnea and quality of life. *Chest*. 2015;147(5):1282–1298; Giovacchini CX, Kessler ER, Merrick CM, et al. Clinical and radiographic predictors of successful therapeutic bronchoscopy for the relief of malignant central airway obstruction. *BMC Pulm Med*. 2019;19(1):219-019-0987-3.)
32. (b) Gas embolism is a reported complication of the use of argon plasma coagulation especially when used with

high flow rates and longer pulse durations. (Reddy C, Majid A, Michaud G, et al. Gas embolism following bronchoscopic argon plasma coagulation: A case series. *Chest*. 2008;134(5):1066–1069.)

33. (d) A hallmark of delirium is the fluctuation of attention levels, with repercussions on attention span, the ability to focus, and short-term memory. With multiple contributors to delirium, caregivers can miss this diagnosis.
34. (c) Patients with cancer on active treatment presenting with an acute ischemic stroke and meeting criteria for intravenous thrombolysis should receive this intervention in a shared decision process.
35. (c) Plateau waves are paroxysmal episodes, self-limited, with motor and autonomic manifestations that can be easily mistaken for seizures.
36. (a) It is rare to see spontaneous ICH with these coagulation parameters. She could have an incipient trauma, or hit her head on the floor after a fall (no clues in history) as the cause for the epidural hematoma. To preserve life and function, a hematoma evacuation is the definitive treatment in this case.
37. (b) Magnetic resonance imaging is the preferred imaging modality for MSCC diagnosis. The need for mobility assistance indicates a deficit that should be evaluated immediately. With a high suspicion for this patient, an MRI would be the appropriate next step to determine the definitive presence and extent of involvement of vertebral body metastasis. The need for mobility assistance indicates a deficit that should be evaluated immediately, rather than referred to outpatient pain management. Zoledronic acid is not used in treatment of MSCC.
38. (c) According to Bilsky's grading system, deformation of thecal sac without cord abutment is classified as Grade 1B. In the absence of mechanical instability, the initial treatment recommendation is radiation therapy. Radiation therapy alone has shown promising results for MSCC in maintaining functionality in the absence of neurological deficits. (Bilsky MH, Laufer I, Fourney DR, Groff M, Schmidt MH, Varga PP, Vrionis FD, Yamada Y, Gerszten PC, Kuklo TR. Reliability analysis of the epidural spinal cord compression scale. *J Neurosurg Spine*. 2010;13(3):324–8; Bilsky MH, Laufer I, Burch S. Shifting paradigms in the treatment of metastatic spine disease. *Spine*. 2009;34(22 Suppl):S101–7.)
39. (d) Loss of sensation, dense paraplegia, and incontinence are late findings of MSCC and signal some degree of permanent disability. While weakness and hyperreflexia are late findings of MSCC, urinary incontinence is the strongest indicator of poor prognosis and permanent disability.
40. (d) In spite of improved surveillance and diagnostic practices, 20% of malignant spinal cord compression occurs in patients without a known malignancy. A patient without a biopsy-confirmed cancer diagnosis in need of corticosteroid treatment presents a dilemma. If there is any question regarding the nature of the lesion, tissue diagnosis must be obtained without delay. Steroids are used with curative intent in treatment of plasmacytomas, thymomas, lymphomas, multiple myeloma, and germ-cell tumors. In these circumstances, corticosteroids given before tissue samples are obtained may cause regression of disease, hindering diagnosis and complicating delivery of definitive chemotherapy. In the absence of neurological deficit, corticosteroids may be withheld pending consultation with neurosurgery and oncologic.
41. (c) The most common hormonal deficit in pituitary apoplexy is a low level of growth hormone. The second most common is an acute deficiency of ACTH. Diabetes insipidus is possible, but uncommon, after pituitary apoplexy.
42. (d) Although the most common cranial neuropathy associated with pituitary apoplexy is dysfunction of the optic nerve caused by compression of tumor against the optic chiasm, this causes visual loss but not diplopia. Ocular motility is regulated by the III, IV, and VI cranial nerves, with the oculomotor nerve being the most vulnerable to pressure effects.
43. (a) Note that the hyperintensity on T1-weighted images lasts only until day 14, when it begins to darken (i.e., become hypointense) as hemoglobin is converted to methemoglobin. In T2-weighted images, where even more time-dependent fluctuation occurs, blood is hyperintense for 24 hours, then hypointense until day 7, then hyperintense for a week, and then after day 14, it has the same hypointensity seen on T1-weighted images after day 14.
44. (e) Use of a dopamine agonist (typically for a prolactinoma) is a predisposing factor to pituitary apoplexy in a small percent of patients, but not a dopamine antagonist. The other four factors listed are all even more common precipitators of apoplexy than is a dopamine agonist medication.
45. (c) This patient is likely presenting with advanced laryngeal cancer. These patients can decompensate due to airway compromise. The airway is best managed surgically in the operating room via awake tracheostomy, and attempted intubation in the ED should be avoided. In the meantime, intravenous steroids can be helpful. In an emergent situation, a "slash" tracheostomy or cricothyrotomy in the ED is warranted.
46. (b) This presentation is highly suggestive of a sentinel bleed from arterial bleeding into the pharynx. Patients

will typically present with brisk but short-lived bleeding from the oral cavity. The workup should be expeditious as bleeding can be catastrophic, particularly in the event of a carotid blowout. The next step in management would be CT angiography to assess for the site of hemorrhage and to guide potential endovascular intervention.

47. (d) A neck mass in an adult should be considered malignancy until proven otherwise. HPV-related oropharyngeal carcinoma in particular may present as a cystic neck mass with minimal symptoms from the primary site, typically in a male in their 50s–60s. A fine needle aspiration (FNA) can confirm the diagnosis. Incision and drainage should be avoided unless malignancy has been excluded.
48. (c) Facial paresthesia is not usually associated with acute sinusitis and suggests cranial nerve involvement, likely by an advanced sinonasal malignancy. Nasal congestion, drainage, and facial pressures are more typical of a patient presenting with acute sinusitis.
49. (c) Dasatinib has been linked to the development of pulmonary arterial hypertension, whereas nilotinib and ponatinib have been associated with an increased risk of myocardial ischemia, cerebrovascular accidents, and peripheral artery disease, in some cases requiring revascularization or leading to amputation. Of note, while the vascular toxicity of nilotinib may be related, at least in part, to its adverse effects on body weight and on glucose and lipid metabolism, the vascular toxicity of ponatinib appears to be a new form of microvascular angiopathy.
50. (b) Adverse cardiac events associated with ICI therapy are rare (less than 1% of patients) but can be potentially life-threatening. The most common and well characterized is ICI-induced acute fulminant myocarditis, which typically occurs within 90 days of initiation of therapy, and is often associated with acute hemodynamic failure and death in up to 50% of patients. The most commonly used and studied are nivolumab, pembrolizumab, and ipilimumab.
51. (d) Patients who develop systolic LV dysfunction (LVEF <50%) during anthracycline treatment should be treated with heart failure goal-directed medical therapy, including beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers. The most studied agents are carvedilol, metoprolol, and bisoprolol, with notable recent trials showing significant reduction of mean change in LVEF using candesartan versus metoprolol and placebo. Statins, aspirin, enoxaparin, and rivaroxaban/apixaban have some clinical trial data to suggest cardioprotection as well. Dexrazoxane, a cardioprotective agent via iron chelation and topoisomerase II inhibition, may be used if cumulative doxorubicin is >300 mg/m^2 and/or the disease is metastatic.
52. (a) Antimetabolites such as 5-fluorouracil, clofarabine, and capecitabine; lomustine + bevacizumab + cyclophosphamide + etoposide; rapamycin, interferon alpha, and trastuzumab have demonstrated ability to cause cardiogenic shock secondary to stress cardiomyopathy, requiring ionotropic agents in up to 20% of patients. Acute stress cardiomyopathy usual occurs with the initial dose.
53. (d) Perform pleuroscopy and pleural biopsy and insert an indwelling pleural catheter (IPC). This patient has an undiagnosed lymphocytic exudative effusion that is recurrent in nature, which requires pleural biopsy to establish a diagnosis. The diagnostic yield of pleural biopsy is ~97%, compared to 62% after two thoracenteses. Given chest discomfort and presence of loculation, he has a nonexpandable, likely entrapped, lung. Talc pleurodesis in this setting will not be successful given loculation. Placement of IPC at the time of pleural biopsy is recommended to control the symptoms. Considering a repeat thoracentesis lacks utility and moreover could lead to additional loculations.
54. (b) There is no evidence that large chest tubes (20–24 F) are better than small bore chest tubes (10–14 F) in the management of pneumothoraces. Although the initial use of large bore chest tubes is not recommended, they may be necessary if there is a large air leak preventing complete re-expansion of the lung. The most common position of the chest tube is mid axillary line. In patients with persistent air leaks, one-way endobronchial valves are an alternative to surgical intervention.
55. (d) Hypercapnic acidosis reduces cyclic mechanical stretch, epithelial injury, and cell death. In ARDS patients with low tidal volume ventilation, permissive hypercapnia is accepted as increase in $PaCo_2$ and subsequent acidosis increases arterial and tissue oxygenation by a right shift of the oxygen–hemoglobin dissociation curve and possibly by increasing cardiac output and circulating catecholamines. Hypercapnic acidosis reduces cyclic mechanical stretch-induced nuclear factor-κB activation, reduces interleukin-8 production, and decreases epithelial injury and cell death compared to normocapnia. However, the rise of the $PaCO_2$ should occur gradually. Rapid rises should be avoided as the negative effects may exceed the beneficial ones (increased heart rate/blood pressure, arrhythmias, and pulmonary vasoconstriction/worsening hypoxemia).
56. (a) Nebulized tranexamic acid. In a randomized study by Wand et al., inhaled tranexamic acid (500 mg TID) showed a significant reduction in hemoptysis com-

pared to the control (96% vs. 50%) over 2 days. There were no adverse events related to the inhalation treatment. TXA when given as inhalation route is more efficacious because of the rapid onset of action compared to intravenous route.

57. (c) The patient is not low risk by Hestia criteria due to homelessness and poor social support. The patient would benefit from admission for social work.
58. (d) The patient demonstrates hemodynamic instability and would benefit immediately from fibrinolysis.
59. (d) The patient is likely Hestia low risk and can safely be discharged on a TSA (target specific anticoagulation).
60. (b) First-time VTE can be a presenting sign of occult, asymptomatic malignancy, but in a well-appearing patient with normal vital signs and no other complaints can be safely managed as an outpatient given Hestia low risk.
61. (g) The differential diagnosis is quite broad, and would include COPD exacerbation, COVID-19, bacterial pneumonia, immune pneumonitis, and pulmonary embolism. However, do not forget that immune checkpoint inhibitors can induce an insulinopenic diabetes mellitus that can lead to diabetic ketoacidosis. The patient would present with tachypnea and shortness of breath due to metabolic acidosis, along with nausea, dehydration, and general weakness.
62. (d) This patient has immune checkpoint inhibitor-induced hypophysitis. Headache is frequently associated with this immune-mediated adverse effect. This patient has central adrenal insufficiency and central hypothyroidism. Hypotension is due to adrenal insufficiency. Lack of reflex tachycardia is due to central hypothyroidism. Hyponatremia is due to both adrenal insufficiency and hypothyroidism. MRI of the sella will reveal pituitary enlargement. Hormonal measurements will reveal central adrenal insufficiency and central hypothyroidism. (El Majzoub I, Qdaisat A, Thein KZ, Win MA, Han MM, Jacobson K, et al. Adverse effects of immune checkpoint therapy in cancer patients visiting the emergency department of a comprehensive cancer center. *Ann Emerg Med*. 2019;73(1):79–87.)
63. (d) Numbness and tingling of extremities and muscle cramping are frequent symptoms of hypocalcemia. Complete thyroidectomy for thyroid cancer has a significant risk for postoperative hypoparathyroidism and the development of hypocalcemia. (Ramirez AT, Gibelli B, Tradati N, Giugliano G, Zurlo V, Grosso E, et al. Surgical management of thyroid cancer. *Expert Rev Anticancer Ther*. 2007;7(9):1203–14.)
64. (a) Stat EKG, and monitor cardiac rhythm while electrolyte abnormalities are corrected with intravenous infusions since the patient has grade 4 hypomagnesemia and is at high risk for cardiac arrhythmia. Hypomagnesemia causes QT prolongation, and thereby increases the risk for torsade de pointes. Hypomagnesemia is caused by the nephrotoxic effect of oxaliplatin, but inhibition of EGFR in the renal tubules by panitumumab also causes hypomagnesemia. (Haroon N, Raza SM, Bhat ZY. Hypomagnesemia and chemotherapy, diagnostic dilemma, and treatment challenge: case report and literature review. *Am J Ther*. 2016;23(4):e1085–90; Oronsky B, Caroen S, Oronsky A, Dobalian VE, Oronsky N, Lybeck M, et al. Electrolyte disorders with platinum-based chemotherapy: mechanisms, manifestations and management. Cancer *Chemother Pharmacol*. 2017;80(5):895–907.)
65. (d) Often times, the bleeding tumor has several areas of active oozing, and mechanical disruption of the friable tumor with the use of a hemoclip may potentially worsen bleeding and is generally not effective for diffuse mucosal type bleeding. Hemoclips are generally avoided in bleeding from tumors unless there is a focal targeted area of hemorrhage, which is rarely the case.
66. (b) False. Overall prognosis should be considered prior to palliative luminal stenting. If patient life expectancy is anticipated to exceed 6 months, a more durable approach such as a surgical bypass (gastrojejunostomy) should be employed. While generally well tolerated, the main complications of gastroduodenal stenting include stent migration, perforation, and stent obstruction by tumor or food. These obstructions can typically be resolved endoscopically by placing a stent within the originally placed stent; however, the potential for re-intervention is higher after 6 months, and therefore, a surgical gastrojejunostomy should be considered in these patients.
67. (c) While TPN has been associated with elevated liver chemistries, it does not cause liver dysfunction, per se, and therefore is not a cause of liver failure. The rest of the listed causes are potential etiologies of fulminant hepatic failure.
68. (d) Patients with asymptomatic jaundice do not require biliary decompression unless their hyperbilirubinemia interferes with chemotherapy (i.e., some chemotherapeutic regimens require a normal bilirubin). Patients with intolerable jaundice or pruritus or poor nutritional status as a result of hyperbilirubinemia should have elective biliary decompression. Pruritus associated with hyperbilirubinemia can be debilitating and has been managed with antihistamines, corticosteroids, cholestyramine, and other medications with only limited success, and relief of obstruction is the mainstay of treatment. Those patients with signs and symptoms of acute cholangitis require urgent drainage and intravenous antibiotics.

69. (a) True. Nonoperative management consists of bowel rest and decompression using a nasogastric tube or long-intestinal tube, analgesia, and antiemetics, if necessary, and it has been showed to be effective in approximately 70–90% cases.
70. (a) Pancreatic cancer accounts for 15–20% cases, and it is the most common cause. It is often diagnosed when advanced, and it is the most frequent cause of gastric outlet obstruction.
71. (b) Neutropenic enterocolitis most commonly occurs 2–3 weeks after receiving cytotoxic chemotherapy when neutropenia is most profound.
72. (d) Systemic sepsis is due to bacterial translocation through inflamed intestinal mucosa. Gastrointestinal bleeding is also common due to damage of the mucosa, which may lead to bowel obstruction.
73. (d) It is crucial to consider the diagnosis of immune-mediated colitis caused by immune checkpoint inhibitors. The number stools per day puts the patient in Grade 3. A CT scan of the abdomen and pelvis is helpful in assessing bowel wall thickening and the extent of bowel involvement and exclude bowel perforation. Exclusion of infectious diarrhea is an integral part of the diagnostic process. The patient will need colonoscopy and biopsy. Empiric treatment with antimicrobials and glucocorticoid needs to be considered. (Rajha E, Chaftari P, Kamal M, Maamari J, Chaftari C, Yeung SJ. Gastrointestinal adverse events associated with immune checkpoint inhibitor therapy. *Gastroenterol Rep (Oxf)*. 2020;8(1):25–30.)
74. (c) These rare types of neuroendocrine cancer of the pancreas cause severe cholera-like diarrhea. The patients are often severely dehydrated with severe electrolyte abnormalities that are unlikely to be managed satisfactorily in the ED setting. Intravenous hydration and electrolyte replacement often require longer than 2 days. Additional intravenous octreotide would help to suppress tumor secretion of VIP. Chemoembolization to reduce tumor bulk often can reduce the symptom burden of diarrhea. (Dreanic J, Lepere C, El Hajjam M, Gouya H, Rougier P, Coriat R. Emergency therapy for liver metastases from advanced VIPoma: surgery or transarterial chemoembolization? *Ther Adv Med Oncol*. 2016;8(5):383–7.)
75. (d) Although the clinical scenario is consistent with acute graft-versus-host disease as the cause of severe diarrhea, infectious colitis and sepsis must also be excluded and empirical treatments need to be initiated immediately. (Robak K, Zambonelli J, Bilinski J, Basak GW. Diarrhea after allogeneic stem cell transplantation: beyond graft-versus-host disease. *Eur J Gastroenterol Hepatol*. 2017;29(5):495–502.)
76. (a) This patient has neutropenic fever and very probably also has neutropenic enteritis. CT scan of abdomen and pelvis is indicated. The epigastric pain can be from inflammation of the transverse colon. Hospital admission is indicated for neutropenic fever in patients with hematological malignancies. (Rodrigues FG, Dasilva G, Wexner SD. Neutropenic enterocolitis. *World J Gastroenterol: WJG*. 2017;23(1):42–7.)
77. (b) Metoclopramide is a prokinetic as well as an antiemetic and would be appropriate in this instance. The patient's nausea should be addressed before any oral laxatives are given. Ondansetron is known to cause constipation; therefore, it is not adequate in this instance. The patient has an unremarkable examination, and it is unlikely that she has a bowel obstruction. Obtaining a plain radiograph to confirm stool burden might be done, but the likelihood of important findings is low. Hydration with IV fluid alone is not appropriate as it is not likely to relieve her symptoms in the ED.
78. (a) Methylnaltrexone is FDA approved for OIC and could be used in the ED subcutaneously as it is fast-acting. Senna and bisacodyl, as well as fiber, are less likely to work in the acute setting and may cause more abdominal discomfort without producing a bowel movement. Disimpacting the patient is not indicated if there is no evidence of impaction on rectal exam.
79. (c) Constipation can sometimes be the only symptom of cord compression. The subtle examination findings of lower extremity weakness with subjective paresthesias should alert the EP to possible spinal cord compression. An MRI of the spine should be ordered urgently. Giving pain medicine to the patients is adequate, but waiting for laboratory results before ordering the MRI is not appropriate. An enema may work, but constipation is not likely the primary cause in this case and missing cord compression can be catastrophic. A CT scan of the abdomen is not appropriate given the normal abdominal exam.
80. (c) This patient is ill appearing and has an examination consistent with peritonitis. He is also febrile and tachycardic. This patient requires immediate resuscitation and evaluation for free air by an emergent upright chest radiograph. While obtaining laboratory testing, ordering a lactic acid, and calling a surgical consult are all appropriate, they are not the most important next step.
81. (d) Drug-induced TMA manifests as a Coombs (−) hemolytic anemia, relative thrombocytopenia, unexplained renal failure, and de novo or worsening hypertension. Systemic manifestations such as low serum haptoglobin level, increased serum lactate dehydrogenase level, and schistocytes may also be present. All of the drugs listed are commonly associated with drug-induced TMA, except ifosfamide.

82. (c) All of the listed interventions are useful in the treatment of MTX toxicity, except dialysis. While dialysis may clear MTX from the blood, there is a rebound effect as MTX if highly protein bound. Dialysis is not effective in removing drugs that are highly protein bound.
83. (a) Patients with SIADH have impaired water excretion due to inappropriate antidiuretic hormone release. Patients with SIADH will excrete all of the sodium content of normal saline, but will retain some of the water, thereby worsening hyponatremia. Patients suspected of possibly having SIADH should not be started on normal saline initially.
84. (a) Allopurinol will prevent the conversion of xanthine to uric acid, but does not help to metabolize already formed uric acid in the bloodstream. However, rasburicase will effectively metabolize uric acid into allantoin. The use of dialysis in the prevention of TLS is controversial. Bicarbonate base fluids may help prevent uric acid deposition in the kidneys, but may also increase the formation of calcium phosphate crystals and worsen kidney function.
85. (d) Sometimes patients will present with urinary retention or new urinary symptoms following prostatectomy catheter removal. Generally, patients should not have a urethral catheter inserted unless the issue is discussed with a urologist due to a concern for traumatizing or further disrupting a recent vesicourethral anastomosis.
86. (c) Clot irrigation can sometimes require 30–60 minutes, and a reasonable attempt should be made to clear the bladder of clot prior to initiating additional treatments. Once the bladder clot has been completely evacuated, consideration is given to initiate CBI. It is important to note that CBI should not be used unless manual evacuation has ensured that large clots have been evacuated from the bladder since these clots are unlikely to clear with CBI alone and may obstruct the catheter during passage.
87. (d) Upper urinary tract drainage is accomplished by ureteral stenting or nephrostomy tube placement. In the infected patient, randomized data have not supported any difference in meaningful outcome such as time to fever resolution. Ultimately, the decision on which to perform is very nuanced and dependent on patient factors. In the patient requiring urgent intervention, the best measure will depend on what is available first. It is known that there is significant regional variation in stent versus nephrostomy tube placement likely for this reason. Contraindications to each decompression method are first assessed. Nephrostomy tubes will generally be contraindicated in those with coagulopathy and may be more difficult in the patient who cannot be placed prone, has morbid obesity, or lacks hydronephrosis. Ureteral stents will not be feasible in the patient who does not have easy endoscopic access to the ureter – in the oncologic setting, this is due to trigonal invasion of a large pelvic mass or due to prior lower urinary tract surgery.
88. (c) Patients presenting after partial nephrectomy with hematuria may sometimes have developed a pseudoaneurysm or arteriovenous fistula. These patients may present with hemorrhagic shock. In the stable patient, initial resuscitation should be commenced and a pseudoaneurysm/AVM can be ruled out with CT angiography. In the unstable patient, urologic consultation should be obtained immediately. Management should be coordinated with urology and will often involve selective angioembolization by interventional radiology.
89. (b) Patients with hypercalcemia often exhibit symptoms such as dehydration, uremia, muscle weakness, diminished reflexes, and cardiac arrhythmias.
90. (a) Febrile neutropenia (FN) is defined as a single temperature of $\geq$ 38.3 °C (101.0 °F) or a sustained temperature of $\geq$38.0 °C (100.4 °F) for at least 1 hour in a patient with an absolute neutrophil count $\leq$ 500 cells/mm^3 or 1000 cells/mm^3 and likely to fall below 500/mm^3.
91. (c) Acute blood loss in a cervical cancer patient may require vaginal packing, volume replacement with crystalloids and/or blood products, and palliative radiation therapy. Invasive procedures such as percutaneous embolization and endoscopic procedures are reserved when noninvasive methods fail.
92. (c) Necrotizing enterocolitis can present with nausea, vomiting, abdominal distension, diarrhea, and hematochezia. On CT classically bowel thickening, mesenteric stranding, mucosal enhancement, and pneumatosis is seen. Supportive measures are the treatment of choice.
93. (d) The most common cause of bone lesions and subsequent pathologic fractures in patients >40 years old is metastatic disease. Imaging should include CT chest, abdomen, and pelvis to identify the site of primary disease. Fractures of the tibial diaphysis should be immobilized in a well-padded long leg splint that goes well above the knee in order to establish rotational control.
94. (a) Total hip replacements most commonly dislocate posteriorly. They result in a shortened, flexed, adducted, and internally rotated limb. Patients often describe standing from a seated position as the mechanism of dislocation. Pending medical stability, closed reduction is safe and effective in the ED. Periprosthetic fractures are not typically associated with standing from a

seated position, but rather, usually occur in the setting of trauma. Buck's traction has not definitively been shown to increase patient comfort.

95. (c) With a history of diabetes, cancer, and recent major surgery, the patient has three common risk factors for necrotizing fasciitis. These patients often present with altered mental status. With the laboratory values listed, she, at a minimum, has a LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score of 9 (≥6 is highly suspicious for the diagnosis). While necrotizing fasciitis often has soft-tissue gas evident on CT scan, this is not always the case. The sooner this patient undergoes surgery, the better her chances of survival.
96. (b) The patient's history and examination are consistent with compartment syndrome. Patients with leukemia are often thrombocytopenic and prone to significant bleeding in the absence of severe trauma. Pain with passive stretch, paresthesias, and firmness on palpation are all consistent with this diagnosis. Absent pulses are a late finding in compartment syndrome. A Stryker needle is not indicated in this case, as the patient is alert and has characteristic examination findings. Further, he has profound thrombocytopenia, and invasive testing could exacerbate the bleeding that likely caused this event.
97. (b) When a maculopapular drug rash presents with fever, lymphadenopathy, or facial edema, drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) should be considered, and a workup for systemic involvement should be performed. The cutaneous eruption is typically maculopapular and rarely presents with purpura, vesicles, or pustules. The liver is the most common site of visceral involvement, but other systemic findings include interstitial nephritis, pneumonitis, myocarditis, arthritis, cytopenias, atypical lymphocytosis, thyroiditis, and cerebritis. The clinical manifestations typically begin 2–6 weeks after initial exposure to the causative medication necessitating a drug history of the past several months when DRESS is suspected.
98. (b) Over 20% of patients treated with anticytotoxic T-lymphocyte–associated protein 4 (CTLA-4) or anti-programmed death 1 (PD-1)/programmed death ligand 1 (PDL-1), and up to 72% with anti-CTLA-4/anti-PD-1 combination therapy develop immune-related cutaneous adverse events (ircAEs), most commonly pruritus and MPR. These ircAEs may be associated with prolonged progression-free survival and overall survival. Unlike MPR to traditional medications, those to immunotherapy may develop at any time during or months after completion of therapy, with a median onset of 62 days (range 1–1676 days) after initiation of therapy. Cutaneous morphology of immune-related MPR may be indistinguishable from that due to traditional medications, or have overlap with lichenoid, psoriasiform, or eczematous rashes.
99. (d) Purpuric eruptions describe nonblanching skin lesions secondary to hemorrhage into the skin. Purpuric lesions may be flat (macular purpura), small and raised (palpable purpura), or larger and netlike (retiform purpura). It is important to recognize the features of macular purpura, palpable purpura, and retiform purpura as the differential diagnosis varies based on these morphologic differences. Macular purpura typically indicates hemorrhage into the skin secondary to low or dysfunctional platelets or vessel wall fragility in the absence of inflammation. Palpable purpura describes small, raised, nonblanching lesions most commonly found on the lower extremities. Palpable purpura is the classic skin manifestation for cutaneous small vessel vasculitis. Retiform purpura describes cutaneous lesions that have a netlike or stellate (starlike) pattern of purpura often with central necrosis or ulceration, reflecting damage to larger vessels with resultant cutaneous ischemia and hemorrhage. Damage to the vessel may occur either through infiltration of the vessel wall or occlusion of the vessel lumen.
100. (a) The SCORTEN severity of illness score for Stevens–Johnson syndrome and toxic epidermal necrolysis includes the following seven criteria: age >40 years, presence of malignancy, heart rate >20, percentage of epidermal detachment >10%, BUN >10 mmol/L, serum glucose >14 mmol/L, serum bicarbonate level <20 mmol/L. A score above 4 predicted >90% mortality.
101. (d) This patient presents with concern for typhlitis. The characteristic sign on ultrasound is a thickened bowl wall, of greater than 3 mm, which can be measured on ultrasound. The remaining imaging findings are all classic signs of other intra-abdominal pathology. The target sign is associated with intussusception, a noncompressible hyperemic blind-ended pouch is appendicitis, a periumbilical cystic structure may be a pancreatic pseudocyst, and the whirlpool sign is associated with ovarian torsion. Of these, typhlitis is the only treatment associated finding that would present with right lower quadrant pain.
102. (b) Patients with Burkitt's lymphoma, particularly those with high tumor burden at, are high risk for tumor lysis syndrome. This is characterized by elevations in potassium, phosphorus, and urea nitrogen. Calcium is typically decreased. There is no definitive effect on sodium.
103. (b) While all of the above are potential treatment complications, most result in mortality during treatment,

whereas pediatric oncologic survivors have a higher than typical rate of suicide.

104. (b) Fatigue, bone pain, fevers, and pallor are all associated with pediatric cancer diagnoses. Weight loss, rather than weight gain, is also a particularly alarming findings in pediatric patients and requires further investigation.

105. (c) Initial management should begin with IV fluid. Although these patients may sometimes appear fluid overloaded with apparent pulmonary edema on chest X-ray, they are usually not hypervolemic, and IV fluids to mitigate the hyperviscous nature of the patient's blood is a key initial treatment. Antibiotics should not be the initial step in management; however, there should be a low threshold to start antibiotics, especially for gram-negative coverage. The patient will most likely be started on hydroxyurea, but initial treatment should be fluids. Patients with moderate-to-severe symptoms benefit from leukapheresis, which this patient may require. At this time, however, initial management is fluid resuscitation.

106. (a) This patient's presentation is concerning for leukostasis, but acute stroke and intracerebral hemorrhage are both high on the differential. A noncontrast CT head can help distinguish between etiologies and is rapidly available. A CT angiogram would not be appropriate as avoiding contrast is preferable in these patients with multiple insults to the kidneys, and whose renal function is likely to worsen with initiation of chemotherapy as tumor lysis syndrome ensues or worsens. In addition, the thrombocytopenia would contraindicate TPA. While brain MRI could also help establish a diagnosis, it takes much longer to obtain and is not as good as CT at identifying blood. This patient may require an MRI in the future if the CT scan is nondiagnostic, but this is not the best initial test. Meningoencephalitis is also on the differential diagnosis for this patient, especially as she may be immunocompromised. An LP could also help establish a diagnosis of subarachnoid hemorrhage. However, CT should precede LP in this patient for both diagnoses, as well as the more likely causes discussed above. Furthermore, this patient is severely thrombocytopenic, and ideally platelet counts should be a minimum of $20x10^3/\mu L$ prior to invasive procedures. If suspicion for meningoencephalitis is high, treatment should be started immediately and not delayed for LP. Seizure and/or postictal state is a less likely cause of altered mental status in this patient given her history, physical examination, and laboratory findings. EEG is of limited utility in the ED and would delay critical workup and management in this patient.

107. (d) This patient is experiencing hyperleukocytosis with myocardial leukostasis, and acute renal failure with severe metabolic acidosis and compensatory tachypnea. In the setting of his renal failure, it is unlikely that his metabolic acidosis will markedly improve and he does not have much more room for additional respiratory compensation. Intubation and ventilation limit his body's metabolic demand and can help decrease the ongoing ischemia while awaiting leukapheresis. Matching the patient's preintubation minute ventilation on the ventilator is important to prevent loss of compensatory respiratory alkalosis causing worsening acidemia and potential hemodynamic decompensation. Although antiplatelets/anticoagulants are the appropriate management for non-ST elevation myocardial infarctions due to acute coronary syndrome, the likely etiology for this patient's ischemia is clogging of his coronary vessel(s) with leukocytes with additional metabolic demands from tachycardia and tachypnea. His thrombocytopenia is a relative contraindication to antiplatelet and anticoagulant therapies, and he is at a high risk for DIC. While consultation to cardiology would be appropriate, initiation of empiric antiplatelet/anticoagulant therapies is inappropriate. Because the patient's main underlying cause of myocardial ischemia is most likely leukostasis, transfusion of packed red blood cells is not recommended as it will worsen the viscosity of the blood and further impair tissue perfusion. While the patient is likely functionally neutropenic and at risk for infection, his current presentation is not consistent with sepsis. Antibiotics may be appropriate if his chest X-ray demonstrates infiltrates or a focal infection is identified, but are unlikely to help his current presentation improve.

108. (b) Although without a clear focal deficit, this patient is altered and has a profound thrombocytopenia, as well as a high risk of DIC, that could lead to spontaneous intracranial hemorrhage that could potentially require neurosurgical intervention. STAT imaging of the brain is required. While this patient's tachypnea could very well be due to respiratory compensation for a metabolic acidosis given his low serum bicarbonate, his blood pressure is robust. While a sodium bicarbonate drip may be in his near future, it would be most appropriate to obtain a pH prior to initiating it in a nonemergent setting. A transfusion of platelets is appropriate in this patient; however, without knowing whether there is a CNS hemorrhage, it is unclear what his platelet goal should be. Transfusion of packed red blood cells, even if bleeding intracranially, is not appropriate as a contained intracranial bleed is not likely to be high volume, the patient is hemodynamically stable, and red blood cell transfusion will worsen blood viscosity and leukostasis. Although the patient's potassium is slightly high and his serum calcium is low, there is no indica-

tion that the patient has any signs of dangerous hyperkalemia, and his hypocalcemia likely exists in relation to his hyperphosphatemia.

109. (b) False: control of cancer-related factor VIII inhibitors does not required tumor control and immunosuppression should be started if tumor resection or other invasive procedures are initiated.
110. (c) L-Asparaginase is associated with low levels of multiple natural anticoagulants especially antithrombin and patients on this drug who have thrombosis should have their antithrombin levels supplemented.
111. (c) JAK2 in patients with myeloproliferative neoplasms is associated with increased risk of thrombosis. In addition, patients with visceral vein thrombosis often have JAK2 mutations – even with normal blood counts.
112. (a) Acquired deficiency of factor V is rare but can be seen in patients with myeloproliferative neoplasms – a clue can be variable elevations of the INR/aPTT.
113. (d) The patient is presenting in aplastic crisis, with a low reticulocyte count and anemia as a result of a reduction in red blood cell production. An infection caused by parvovirus is often a source of aplastic crisis, and antibiotic therapy is not useful. Exchange transfusion is typically reserved for acute chest syndrome and does not increase the hemoglobin concentration. Oxygen is not beneficial unless the patient displays signs of hypoxia. The patient is most helped by a transfusion of red blood cells to improve her condition.
114. (a) Avascular necrosis is a complication of sickle cell disease. Progressive occlusion of microcirculation leads to increased intraosseous pressure and cell death. A fracture is more likely to occur in the setting of some trauma. Osteomyelitis typically presents with fever and may also have skin changes. The patient is otherwise young, and a tumor is not at an increased risk for tumor production.
115. (d) Laboratory workup is typically not required when the provider is familiar with caring for patients with sickle cell disease who are suffering from an uncomplicated pain crisis. However, laboratory testing should be considered when the patient is being admitted, another diagnosis is suspected, if the patient appears unwell, or if the provider suspects worsening anemia.
116. (a) The patient is presenting with acute chest syndrome, and the classic triad of acute chest syndrome includes fever, hypoxia, and pulmonary infiltrate. Acute chest syndrome often presents with chest pain, shortness of breath, and dyspnea on exertion. Occlusion due to sickling in the pulmonary vasculature causes the patient to become hypoxic, which drives more sickling to occur, which in turn causes more occlusion due to sickling.
117. (b) This patient presents with what appears to be acute lymphoblastic leukemia. It is not uncommon for a patient with acute leukemia to be seen in the ED prior to diagnosis. Although his overall white blood cell count may be elevated, his ANC is <500, and has been so for an unclear amount of time. This is severe neutropenia, and he is at risk for infection due to many pathogens. The patient's headache, ocular exam, and CT findings are all concerning for acute invasive fungal sinusitis. This is an infectious disease emergency and he needs rapid initiation of antifungal therapy. While an MRI may be obtained for characterizing and surgical planning, he needs urgent stabilization now. Both micafungin and amphotericin are antifungal therapies. Micafungin has activity against *Candida* spp. and *Aspergillus* spp. However, it notably does not cover other molds, such as the Mucorales. Amphotericin has broader antifungal coverage that includes molds and dimorphic fungi. Posaconazole, which was not an option, is also a reasonable empiric treatment for acute invasive fungal sinusitis. Finally, pathogenic diagnosis typically requires nasal endoscopy and sinus evaluation by a trained otolaryngologist. Nasopharyngeal swabs are unlikely to recover the offending pathogen and are not used for diagnosis.
118. (a) This is a neutropenic patient presenting with significant abdominal pain. The differential is broad but would include neutropenic enterocolitis, also known as typhlitis. Other considerations would be enteroinvasive pathogens such as *E. coli* or *Shigella* or other causes of colitis (viral, ischemic, etc.). Further, she notes recent decrease in diarrhea, which could be the natural course of illness but also raises flags for possible bowel obstruction, particularly in a patient with intra-abdominal malignancy. CT scan would help to narrow this differential and is the preferred modality for diagnosing neutropenic enterocolitis. In patients with neutropenic enterocolitis, antibiotics should be targeted toward gram-negative and anaerobic bacteria, which are commonly found in the gastrointestinal tract. Resistant gram-positive bacteria, including *Enterococcus*, typically are not involved. While some infections or illnesses will require G-CSF, this should not be a priority until the diagnosis and trend of neutropenia is known. Finally, while she is at risk for *C. difficile* colitis, this is a less common cause of hemorrhagic colitis.
119. (c) The patient is at high risk for central line-associated bloodstream infection (CLABSI) in addition to other infection syndromes associated with receiving cytotoxic chemotherapy. Gram-positive bacteria including *S. aureus*, coagulase-negative staphylococci, and

Enterococcus are common pathogens associated with CLABSI. In addition, the patient is receiving total parenteral nutrition which places her at increased risk for CLABSI due to *Candida* species. A comprehensive workup for undifferentiated fever in an oncologic patient in the ED should *begin* with a complete blood cell count, metabolic panel, and at least 2 blood cultures from separate peripheral sites. Recognizing that peripheral access can be difficult to accomplish in some cases, one set can be drawn from the central venous catheter when necessary. Blood cultures obtained from catheters have traditionally been associated with higher contamination rates than those obtained from peripheral venipuncture. Obtaining 2 sets of blood cultures from the central venous catheter increases the risk of blood culture contamination, which can lead to an incorrect diagnosis of CLABSI and unnecessary removal of the central venous catheter, particularly if coagulase-negative staphylococci are isolated. It is appropriate to start empiric broad-spectrum IV antibiotics, but after blood cultures have been obtained to guide diagnosis and treatment. As the patient is hemodynamically stable, additional workup for CLABSI can be completed prior to discussion with the patient's oncologist and deciding whether catheter removal is indicated to achieve source control.

120. (d) A history of high-dose corticosteroid use for GVHD coupled with the indolent onset of respiratory symptoms and lack of appropriate antibiotic prophylaxis raises the concern for *Pneumocystis jirovecii* pneumonia, which is supported by the chest radiograph findings. The patient reports compliance with taking valganciclovir, which provides effective prophylaxis against CMV and HSV infection. While he is not on prophylaxis for *Pseudomonas*, the typical presentation for Pseudomonas pneumonia would involve a more acute presentation and likely more localized infiltrates.
121. (d) There is no validated risk stratification tool for pediatric febrile neutropenia. Therefore, in the majority of cases, patients are admitted for a period of inpatient observation.
122. (c) It is suspected 80% of infections arise from endogenous flora.
123. (a) For safe discharge, a patient should live no more than 1 hour or more than 30 miles away from the clinic or hospital.
124. (c) Oral antibiotics are noninferior to intravenous antibiotics in cases of low-risk febrile neutropenia. This is true for both solid and hematologic malignancies.
125. (b) Evaluation for potential alternative causes should be performed in most cases. CT is recommended in this instance to help diagnose and characterize the extent of disease as well as rule out other causes. Ultrasound cannot offer a definitive diagnosis.
126. (b) Persistent GI bleeding coupled with other clear surgical indications including abdominal free air. Involvement of the cecum is likely given its limited vascular supply; however, its involvement alone is not an indication for surgery. Degree of bowel wall thickening alone is also not an independent indication for surgery.
127. (c) Route of chemotherapy administration plays no role in neutropenic enterocolitis. All other elements are potential risk factors, especially timing from last chemotherapy (between days 12 and 17). Tumor types tend to be solid in adult and hematogenous in pediatrics.
128. (a) Recombinant granulocyte colony-stimulating factor (G-CSF) may be beneficial; however, data regarding its success have been mixed and it has not shown a reduction in mortality from neutropenic enterocolitis.
129. (b) Three domains of psychosocial model are the predisposing factors, precipitating factors, and perpetuating factors. Predisposing factor is the genetic makeup which makes the basis of vulnerability. Precipitating factor is the ongoing challenges, like substance misuse. Perpetuating factor is an acute event, such as loss of a loved one, that pulls the trigger.
130. (d) In addition to general risk factors of suicide, such as depression, they have the burden of adverse effects of cancer treatment. This may include physical symptoms such as intolerable pain and extreme fatigue. Cancer patients may face other challenges such as altered body image, role reversal, and loss of job which adds to their burden.
131. (a) Poor sleep, fatigue, and weight loss may be present in depression as well as in cancer patients undergoing treatment. Hopelessness and loss of interest in previously enjoyable activities are the key features of depression.
132. (c) First step in managing suicidal patients is his/her safety. Making sure he has no access to any weapon. Everything listed in the question is also essential. Patient should have a follow-up plan, needs an antidepressant and also a hot line number, but removing access to weapon remains the first step.
133. (c) Hypoactive delirium is more frequent than the hyperactive (agitated) type in cancer patients, and it is frequently missed. Most cases of delirium in cancer patients are of the mixed type, which has features of both, hyperactive and hypoactive. All other choices are correct.
134. (d) Although all are causes of delirium in cancer patients, medication's side effects are the most com-

mon. Opioids are the most common, followed by benzodiazepine and anticholinergic medications.

135. (d) Safety of the patient is the most important step in management of delirium as in the case discussed in the beginning of this chapter. Patients with delirium are at risk of hurting themselves or medical staff particularly nurses. Delirious patients may experience frequent falls and may pull IV lines.

136. (b) Refractory delirium is the most common reason for palliative sedation. The purpose of sedation is to control refractory symptoms and not to hasten death. The need to continue sedation should be evaluated frequently, and if symptom has improved, sedation should be weaned off or stopped. Palliative sedation should be differentiated from euthanasia.

137. (d) There are two types of transalar herniation: ascending and descending. Ascending transalar herniation occurs as a result of middle cranial fossa mass effect, leading to superior and anterior temporal lobe displacement across the sphenoid ridge. Descending transalar herniation results from frontal lobe mass effect, leading to posterior and inferior displacement across the sphenoid wing. Transalar herniation can lead to infarction in both ACA and MCA territories secondary to mass effect on the carotid terminus. Subfalcine herniation can cause ipsilateral ACA infarction, and uncal herniation can cause ipsilateral PCA infarction.

138. (e) Massive hemoptysis is defined as expectoration of ≥300–600 mL of blood within a 24-hour period. Pulmonary TB is the most common cause of massive hemoptysis worldwide. Bronchogenic carcinoma is the most common malignant cause of massive hemoptysis. Trauma, postoperative complications, and pulmonary fibrosis are not common causes of massive hemoptysis.

139. (d) Hounsfield unit is a relative quantitative measurement used to interpret radiodensity in CT relative to water, which has a HU of 0. Blood is slightly denser than water with a HU range of 30–60 (depending on its state, e.g., clotted, liquid, acute, subacute). Less dense materials such as air and fat have a HU of −1000 and −100, respectively. Bone is significantly denser, with cortical bone having an approximate HU of 1000.

140. (b) Radiographs are relatively insensitive to detecting lytic lesions compared to cross-sectional imaging such as CT or MRI. Radiographs can identify lytic lesions after loss of 30% or more of bone mineral density. Therefore, normal radiograph findings in setting of high clinical concern for a lytic lesion often warrant further evaluation with cross-sectional imaging.

141. (b) The patient described here presents with an examination and vital signs that are consistent with septic shock. Visualized in the ultrasound image is a kidney which demonstrates hydronephrosis, given to be unilateral. In nononcologic patients, unilateral hydronephrosis is often associated with obstructive ureterolithiasis; however, in oncologic patients, it may also be associated with tumor compression of the ureter. The resulting backflow of urine to the kidney results in dilation of the renal calyx, which can be visualized directly with ultrasonography. Source control in this instance requires placement of either a ureteral stent or a nephrostomy tube to drain the obstructed kidney. Choosing dobutamine is incorrect, but would be considered if a bedside echocardiogram showed significantly decreased LV ejection fraction. A surgical consultation may be indicated in cases where the patient has free fluid within the abdomen suspected to be hemorrhagic in source, or if there were signs of malignant bowel obstruction. There is no indication of massive thromboembolism, which might be considered if bedside sonography shows septal flattening, McConnell's sign, or if the patient is known to have PE with decompensation. A CT should not be considered as the patient has unstable vital signs and would not benefit from awaiting an unnecessary imaging studies.

142. (e) The patient in this scenario presents with nonspecific symptoms common to the oncologic population. Historical features of his pain suggest pericarditis, but this description is not always consistent, and the classic findings of JVD, muffled heart sounds, and pulsus paradoxus are frequently missed on physical examination. His echocardiogram, however, clearly shows a pericardial effusion with right atrial inversion, a finding concerning for pericardial effusion with tamponade. Despite the patient's stable vital signs, he is at high risk for decompensation, and pericardiocentesis should be performed, ideally in a controlled environment with experienced operators, but in the ED if any instability develops. The other options describe the management of massive pulmonary embolus, another etiology of obstructive shock but with different management; ST-segment elevation MI, which is unlikely given the described ECG and patient presentation; pneumothorax and massive pleural effusion for which there is no evidence.

143. (b) The patient presents with unilateral leg swelling. There are multiple causes of edema but, given the asymmetric pattern seen here, a localized pathology rather than systemic pathology is more likely. Deep venous thrombosis (DVT) should be one of the first diagnosis to consider in an emergency setting especially in a patient with risk factors. The patient in this scenario has breast cancer and is undergoing chemotherapy which puts her at higher risk for venous throm-

boembolism. Additionally, she is presenting with leg swelling, tenderness, and overlying skin changes which makes DVT more likely. Using a risk stratification score such as the Well's score, the patient will be scored 4 out of 9, placing her as a high risk for DVT. One of the important sonographic characteristics for DVT is finding a noncompressible vein containing an intraluminal echogenicity which represents a thrombus. Of the choices given, B and C are the only describing venous findings. Of these two choices, B is consistent with DVT as the vein is found to be noncompressible indicating the presence of a thrombus.

144. (a) This patient has clinical signs of heart failure (hypoxia, JVD, symmetric bilateral lower extremity edema along with dyspnea) and is on a chemotherapeutic agent (doxorubicin) that is known to cause cardiotoxicity. The ultrasound findings of diffuse B lines, bilateral pleural effusions, and a decreased left ventricular ejection fraction coupled with her clinical signs and symptoms would confirm the diagnosis of heart failure.
145. (b) Duloxetine. Studies evaluating gabapentin and acupuncture have been conflicting or not shown improvement for chemotherapy-induced peripheral neuropathy (CIPN). Gel formulations have shown promise but the agent with the best evidence for use in CIPN is duloxetine. In 2013, a trial looking at CIPN caused by paclitaxel or oxaliplatin showed improvements in outcomes compared to placebo.
146. (a) Hyaluronidase is indicated for extravasation of vinca alkaloids. In addition, the arm should be elevated and a warm compress rather than a cold compress should be applied. Plastic surgery consultation is only indicated for a large volume vesicant extravasation; severe pain, if healing has not occurred 1–3 weeks after extravasation; or if there is early necrosis present.
147. (c) Epinephrine is recommended for the treatment of anaphylaxis in all current guidelines and injection into the thigh results in more rapid and higher plasma levels than other IM locations. Steroids and antihistamines are considered adjunctive therapy for anaphylaxis.
148. (b) SIADH with severe hyponatremia can occur after only one dose of cyclophosphamide. In addition, the patient is also on sertraline, which can also contribute to SIADH. She likely does not have brain metastasis and the recent MRI was negative. There are no signs of trauma or infection.
149. (d) The mechanism associated with the impact of radiation therapy on the heart and blood vessels is driven by inflammation related to the trauma of injury coupled with late fibrosis and functional instability. Intimal damage to cardiac vessels followed by cell proliferation in a disorganized manner can lead to premature coronary artery disease and atherosclerosis. Damage to cardiac valves can lead to late fibrosis and calcification, which are able to cause both stenosis and insufficiency. Myocardial and pericardial inflammation can lead to muscle dysfunction, cardiomyopathy, and congestive heart failure. Pericarditis can be seen in situations where a large volume of heart receives radiation therapy and acute inflammation can lead to constriction of function. Electrical conduction deficits are seen and thought to be related to fibrosis in conduction pathways. Multiple chemotherapy agents influence cardiac health, and their relationship to injury imposed by radiation therapy remains under evaluation.
150. (d) Acute radiation effects to tissues are influenced by total radiation dose, daily treatment dose (fractionation), and volume of tissue treated. This information is often not immediately available to emergency departments when patients present for evaluation as specific treatment documentation is often in the department shadow record and not directly integrated into electronic healthcare records. The volume of the treatment target influences the number of stem cells directly affected from daily treatment. Daily treatment dose also influences injury to stem cells. Hence, total and daily doses as well as target volume are all directly related to the development of sequelae from the treatment.
151. (a) True. There are reports of radiation injury to the lung tissue outside of the radiation treatment field. Although felt to be spurious at initial review, investigators have suggested that production of nitric oxide gas as a by-product of radiation-induced injury may play a role in generating injury in other parts of pulmonary parenchyma not directly in the radiation therapy treatment region.
152. (b) False. The mechanism of injury is multifactorial as radiation therapy likely has impact in all compartments of the kidney including the glomeruli, mesangium, and endothelium.
153. (a) True. At very high single-fraction total body doses (>10 Gy), death will occur through cerebrovascular syndrome in spite of support within 24–48 hours. The syndrome is due to uncontrollable swelling within the central nervous system associated with compromise of all neuromuscular processes. At total body doses of 5–12 Gy, death without support will occur in 1–2 weeks due to denudation and destruction of the gastrointestinal system associated with profound fluid loss and diarrhea. These cells have a self-renewal capacity measured within a few days; thus, a single total body dose of 10 Gy will eliminate a large portion of the stem cells within the gastrointestinal crypts. Although this dose does not affect differentiated adult cells, the exposure

eliminates the self-renewal potential of the stem cell; therefore, the mucosal surface of the gastrointestinal tract becomes denuded with no barrier for fluid and blood loss within a short period of time, measured in days. At total body exposure doses of 2–5 Gy, death will occur from damage to the hematopoietic system with primary damage to progenitor cells inhibiting self-renewal. Lymphocytes may die an intermitotic death, and this finding may be a surrogate biomarker for acute exposure within the first few hours to days of an incident. However, by day 30, most circulating blood elements are depleted with death often attributed to infection. The term, LD (lethal dose) 50/30, is borrowed from our pharmacology colleagues and reflects the LD of an agent that will cause 50% mortality in 30 days. Although radiation is not a drug, the LD 50/30 is now generally thought to be 5 Gy with modern hospital support.

154. (a) True. At total body exposure doses of 2–5 Gy, death will occur from damage to the hematopoietic system with primary damage to progenitor cells inhibiting self-renewal. Lymphocytes may die an intermitotic death, and this finding may be a surrogate biomarker for acute exposure within the first few hours to days of an incident.
155. (b) False. The use of bone marrow transplant in this setting remains controversial with strong advocates on both sides of the question.
156. (e) The pediatric population is at high risk of developing therapy-related mucositis. Ninety-nine percent of pediatric patients undergoing hematopoietic stem cell transplant will experience oral and/or gastrointestinal mucositis.
157. (c) The largest contributor to increased medical costs for patients with mucositis is extended inpatient hospitalizations, which can occur as a result of the potential sequelae of mucositis, such as infection or nutritional deficiency. A report based on data from 2012 estimated a combined cost of $15,500 for every inpatient hospitalization due to severe mucositis.
158. (a) Benzydamine is currently the only agent for which there is level 1 evidence supporting its use in the management of mucositis. Benzydamine mouthwash can be used both for the prophylaxis and treatment of oral mucositis in patients receiving chemotherapy alone, radiation treatment alone, or concurrent chemoradiation to the head/neck.
159. (c) Significant risks associated with mucositis include severe infections, dehydration, and weight loss, requiring hospitalization. Such infections and severe malnutrition result in unexpected treatment breaks or premature discontinuation of antineoplastic therapies and are associated with increased rates of recurrence and worse survival. Patients should be monitored closely with additional nutritional support including a feeding tube if needed and routine IV hydration.
160. (e) Leukoreduced and irradiated blood products should be given to all HCT recipients due to the risk of transfusion-associated GVHD, which is associated with high mortality.
161. (c) Splenic rupture is a rare but catastrophic complication of high-dose G-CSF.
162. (c) The patient's symptoms may be explained by mild acute GVHD (grade II) involving GI tract. Endoscopic studies should be performed to provide histologically corroboration the clinical suspicion and to rule out viral infection (particularly CMV).
163. (a) The most likely diagnosis is ICANS based on the clinical scenario. The ICE score is a 10-point score that can help the clinician to grade ICANS and further management based on grading.
164. (b) The differential diagnoses include acute coronary syndrome, pulmonary embolism, and immune-mediated myocarditis.
165. (d) Enasidenib is an inhibitor of isocitrate dehydrogenase 2 (IDH2) and can cause a differentiation syndrome that resembles sepsis. It is important to discuss with the oncologist and consider treatment with potent glucocorticoids.
166. (d) Blinatumomab is a bi-specific antibody that can cause an infusion reaction syndrome. Blinatumomab links T cells and malignant B cells and activates the T cells to exert cytotoxic effect on the malignant cells. Blinatumomab also causes a cytokine release syndrome. These leukemic patients are often neutropenic, and neutropenic fever is also likely.
167. (c) More than 1 ED visit in the last 30 days of life. Researchers used administrative healthcare data to describe this key indicator.
168. (d) 30%. It is impossible to have a system where the ED visit rate is zero, given it is entirely appropriate for individuals to visit the ED at the EOL for issues that arise; however, when administrative health data are used to examine systems and health policies, a rate of 30% is accepted as the benchmark for EOL ED visits.
169. (a) Fever. In a study that examined 18 EDs in the United States, pain, shortness of breath, nausea, and abdominal pain were found to be the most common ED diagnoses.
170. (c) Shorter survival. It is a common misconception that palliative care services lead to a faster death; however, studies show that access to early palliative improved quality of life and relieves suffering, without necessarily hastening death and even longer survival.
171. (a) Opioid analgesics have many potential side effects that may make patients or prescribers reluctant to use

the medications or use them in adequate doses to achieve pain control. Patients can develop a tolerance to certain side effects (e.g., nausea or respiratory depression); however, other side effects (e.g., constipation, pruritus) are not decreased with chronic use.

172. (b) Anticonvulsants such as gabapentin and pregabalin require close follow-up for titration. Peritoneal carcinomatosis generally causes visceral pain. Topical lidocaine patches should be worn for 12 hours and then removed for 12 hours. Corticosteroids are often used as adjuvants to treat a variety of pain types and have analgesic effects on pain from bony metastases and neuropathic pain.
173. (c) Opioids, with the exception of methadone, follow first-order kinetics and achieve their peak plasma concentration (and maximal analgesic effect) along a similar timeline: 60–90 minutes for oral/rectal administration, 30 minutes for subcutaneous/intramuscular administration, and 6–10 minutes for intravenous administration.
174. (c) For those patients in more severe pain, or requiring intravenous dosing for other reasons (difficulty swallowing), there are many available intravenous opioids. For the opioid-naïve patient, morphine is a safe, standard drug to start therapy. However, morphine should be used with caution in patients with renal impairment because one of the active metabolites (morphine-6-glucoronide) can accumulate with renal dysfunction. For intravenous dosing of the opioid-naïve patient, a starting dose of 2–5 mg of morphine (or equivalent) is recommended. This dose should be followed by a reassessment at 15 minutes, and if the pain score remains unchanged or increased, the initial dose given should be increased by 50–100%. If the pain score is decreased but still moderate (e.g., 4–7), the same initial dose should be repeated, and if the pain level is low (e.g., 0–3), then the initial dose can be used as needed.
175. (b) Pharmacologic agents to ease constipation are typically divided into five categories: bulk-forming agents, softeners, stimulants, osmotic agents, and peripheral mu-opioid receptor antagonists. Bulk-forming agents increase fecal mass to stimulate peristalsis. Stimulants act by increasing intestinal motility, whereas osmotic agents (e.g., polyethylene glycol, lactulose) act by increasing water content in the large bowel. The NCCN recommends prophylaxis with both a stimulant (or prokinetic) agent and the osmotic agent polyethylene glycol. Bulk-forming agents and stool softeners are unlikely to be effective in isolation. A 2010 Cochrane review recommended the use of polyethylene glycol over lactulose for chronic constipation because of better outcomes related to stool frequency, form, associated abdominal pain, and use of additional products. If constipation persists despite the above medications, the provider can titrate the existing regimen or add an additional agent, such as magnesium hydroxide. Two peripherally acting mu-opioid receptor antagonists may be considered if laxative therapy has failed. Both methylnaltrexone, administered subcutaneously or orally, and naloxegol, an orally active agent, have demonstrated efficacy in reversing opioid-induced constipation.
176. (a) Younger age is a risk factor for substance abuse disorders.
177. (c) If a person engages in aberrant behaviors with their opioids in response to poorly controlled pain long enough, they can become actually addicted. In secondary alcoholism, it is recognized that if a person uses alcohol to self-medicate panic disorder long enough, they can develop alcoholism in addition to their panic disorder.
178. (d) Only 30% had chart documentation suggesting a major need to improve recognition, diagnosis, and documentation of alcohol problems in people with advanced medical illness.
179. (b) Actually, longer drinking histories are predictive of a good response. When one sees these characteristics among others that predict a good response, it is clear why some patients undergoing cancer treatment who want to be able to adhere to their oncologic treatment may be good candidates for Antabuse.
180. (c) Morphine is the first-line agent for dyspnea in dying patients, particularly those whose goals are strictly focused on comfort. Intubating the patient is not in line with his expressed wishes and goals of care. BIPAP can be a useful tool at the EOL and can be considered, but morphine is still first line.
181. (b) Noninvasive ventilation can be a helpful tool for patients with dyspnea near the end of life, particularly if the underlying etiology of the patient's dyspnea is reversible. For some, it can help them through the acute crisis and improve dyspnea. In others, it is burdensome and may simply prolong dying.
182. (d) The etiology of dyspnea at the end of life is complex and often multifactorial. Some causes are treatable and reversible, while others are not.
183. (c) Palliative extubations are medically and ethically appropriate when the patient's condition and goals are not aligned with the use of mechanical ventilation. The process of extubation is relatively straightforward and within the purview of the emergency provider.
184. (b) Heyland et al. found that only 2.7% of hospitalized end-stage cancer or other advanced diseases understood that actual CPR success rates were <10%. (Heyland DK, Frank C, Groll D, Pichora D, Dodek P, Rocker G,

et al. Understanding cardiopulmonary resuscitation decision making. *Chest*. 2006;130(2):419–28.)

185. (e) The reality of what may occur during resuscitation differs than what is usually depicted in movies or on television in which many instances of resuscitations are shown to be successful.
186. (d) According to Giza et al., cardiac arrest is the most frequent precipitating cause in hospitalized patients requiring CPR. (Giza DE, Graham J, Donisan T, Balanescu DV, Crommet J, Botz G, et al. Impact of cardiopulmonary resuscitation on survival in cancer patients. Do not resuscitate before or after CPR? *J Am Coll Cardiol CardioOncol*. 2020;2(2):359–62.)
187. (a) Several studies show that in patients with solid tumors, unexpected cardiac arrest may be related to reversible problems, and those patients may be more responsive to CPR. (Giza DE, Graham J, Donisan T, Balanescu DV, Crommet J, Botz G, et al. Impact of cardiopulmonary resuscitation on survival in cancer Patients. Do not resuscitate before or after CPR? *J Am Coll Cardiol CardioOncol*. 2020;2(2):359–62.)
188. (f) All elements above are essential to goals-of-care conversations. (Ouchi K, Lawton AJ, Bowman J, et al. Managing code status conversations for seriously ill older adults in respiratory failure. *Ann Emerg Med*. 2020:S0196-0644(20)30410-8. doi: https://doi.org/10.1016/j.annemergmed.2020.05.039. Epub ahead of print.)
189. (e) Palliative care applies to *all* phases of a life-limiting condition and is not just for dying patients. In fact, maximal benefit is likely when there is early integration of palliative care into management plans as opposed to only considering such care as a last resort measure when "no more can be done" for the patient. The early integration of palliative care is associated with a higher quality of life, including better understanding and communication, access to home care, emotional and spiritual support, well-being and dignity, care at time of death, and lighter symptom burden. In fact, some evidence suggests that, on average, palliative care and hospice patients may live longer than similarly ill patients who do not receive such care. Palliative care also has the ability to simultaneously improve quality and control the cost of care for the most seriously ill patients.
190. (c) Spiritual care personnel are often fully initiated into palliative care services and serve as valuable champions to link existing resources to ED initiatives. It is important to begin an ED-PC initiative with identified ED "champions" who can effectively build upon lessons learned from other prior successes and failures so that the initiative is tailored to fit the unique ED setting. Integration initiatives in the ED may have a higher chance of success when ED champions are fully engaged with palliative care experts to collaboratively define not only resources and processes but also appropriate metrics to track outcomes and measure impact of the integrated initiative.
191. (c) Oxygen and antibiotics are appropriate interventions while initiating efforts to define prognosis and goals of treatment.
192. (a) Bowel obstruction in patients with advanced cancer is rarely a surgical emergency and typically allows time to consider multidisciplinary aspects of the patient's condition. Palliative care specialists can provide valuable input into the appropriate goals of care. Previous treatment, cancer stage, and prognosis are unique variables to consider in cancer patients with gastrointestinal obstruction. Although accurate prognostication is difficult, it is helpful to attempt to determine if a patient can recover from abdominal surgery and obtain a meaningful quality of life prior to death from their malignancy.
193. (e) Patients may be referred for hospice services if their illness physiologically meets criteria of a prognosis of 6 months or less, should the illness run its usual course, and after counseling regarding the implications of this prognosis and available options, have accepted this prognosis and elect a treatment regimen and plan of care which focuses only on comfort-based treatments and services.
194. (d) The patient clearly has difficult to control symptoms requiring frequent nursing assessments indicating the need for inpatient unit level of care.
195. (b) However, a caveat should be made that there are some "bridge" programs that allow the patient to pursue treatment while receiving some hospice benefits. In addition, some commercial insurance plans may evaluate specific treatment requests in conjunction with hospice care. This is really where nuances can be quite intricate and worthwhile to explore directly with the medical director of the hospice of the patient's choice with palliative care team assistance.
196. (d) The patient has severe, ongoing symptoms that warrant further management with possible parenteral medications and ongoing frequent nursing assessments to stabilize her comfort and treatment regimen that would not be possible in a routine level of care. Continuous care is meant for the short-term stabilization of a new symptom which is likely to be controlled quickly, typically in 1–2 days; however, it is unlikely that she will have her symptoms stabilized in the setting of an acute obstruction with need for ongoing medication titration and assessment of NGT management. Calling the patient's hospice and reviewing her presentation and current goals would likely facilitate this transfer.

197. (d) All these examples are great for guidance on ethical dilemmas; none of them can "always" have guidance for every situation that can occur.
198. (a) Values are an acquired set of norms that individuals, groups, and organizations use as standards to measure others. While some values are pervasive, there is no uniform set of values across all individuals and groups.
199. (c) In an emergency, not all relevant information is available at the time important decisions must be made.
200. (d) Ethical problems can often take some time to work out, but a rapid approach rarely has enough time for a formal ethics consult. Buying some time so a reasonable solution can be derived is often the best that can be done.
201. (b) Sexual minorities consistently have less access to healthcare, are less likely to be insured, and are more likely to live in poverty.
202. (d) The minority stress model explains that minority groups experience chronic high levels of stress from stigmatization that can contribute to poor outcomes and disparities.
203. (d) For the three leading causes of cancer death in the United States, colon, breast, and lung cancer, survival rates for Blacks lag those for Whites.
204. (c) Provider and systemic bias can either be explicit or implicit. Explicit bias is often easier to recognize as the outward expression of prejudice. Implicit bias, the unconscious attribution of qualities or values to a member of a certain group, can be much more difficult to recognize.
205. (d) Many physicians have different exposures and backgrounds than the patients they serve. Unconscious attitudes and stereotypes affect behaviors and decisions in healthcare. In order to have greater awareness of bias in patient care, it is critical for physicians to receive education, feedback, and coaching on equitable practice. Patients with schizophrenia are 1.5–2 times more likely to die of their cancer than patients without mental illness. Patients with schizophrenia are also more likely to present at advanced stages of disease, are offered surgery at a lower rate, and receive fewer chemotherapy sessions. Patients with schizophrenia and other disabilities are often unable to advocate for themselves and are also at increased risk of experiencing physician bias.
206. (c) The second step of the WHO analgesic ladder includes opioid for mild-to-moderate pain as well as nonopioids and adjuvant drugs.
207. (e) A simple way to classify different types of pain is whether they are related to tissue damage (somatic nociceptive, visceral nociceptive) or nervous system disorders (neuropathic). The sympathetic nervous system may play a role in exacerbating pain through activation of the sympathetic nervous system.
208. (c) Methadone can be difficult to administer in the acute setting, given that its peak effect on respiration can occur later than its peak analgesic effect.
209. (c) Tramadol is a mixed-mechanism drug that acts as a weak mu-opioid receptor agonist, but also demonstrates some norepinephrine and serotonin reuptake inhibition.
210. (e) As of early 2020, neither the American College of Emergency Physicians nor the American Academy of Emergency Physicians have formed such groups.
211. (f) All are challenges to developing such quality metrics. Many of these factors stem from substantial shortcomings in the funding, oversight, and coordination of measure development and public reporting for cancer care.
212. (c) The first patient navigator program was created by Harold Freeman in 1990 at Harlem Hospital in New York. He focused on underserved women with breast cancer. The goals of the program were to expand access to cancer screening, improve clinical follow-up among medically underserved women through community outreach, and reduce the time between an abnormal test result and diagnosis and/or treatment. Eliminating barriers to health access, such as lack of insurance or cultural and communication barriers, were also critically important. The navigation program was remarkably successful.
213. (d) The American Nurses Association recognized emergency nursing as a specialty practice in 2011. As a challenging and unique profession, this clinical practice area prepares nurses to provide prompt interventions to stabilize or prevent further patient deterioration. The fast-paced, high-acuity setting commands refined critical thinking, clinical assessment, communication, and prioritization skills.
214. (f) Oncologic social workers routinely address all of these stressors for cancer patients.
215. (d) Gamma rays are emitted from unstable nuclei as part of radioactive decay.
216. (b) Geographically, the South has 40% of screening-eligible patients, but has the lowest density of ACR-designated screening centers, and a 3.5% screening rate. In contrast, the Northeast has the lowest eligible percentage (15.5%) but the highest density and screening rate (10.1%). While gays, lesbians, and bisexuals have higher rates of smoking (thus higher proportions that are screening-eligible), they receive LCS at rates similar to their heterosexual counterparts. The landmark National Lung Screening Trial (NLST) demonstrated mortality reduction with lung cancer screening for the first time. The NCI-sponsored 1986 Mayo Lung Project found no benefit in overall mortality for lung cancer screening. Other contemporaneous NCI trials at

Memorial Sloan Kettering and Johns Hopkins also failed to find mortality benefits.

217. (b) The most common primary cancer affecting the orbit in adults is lymphoma. Orbital lymphoma can be the extranodal manifestation of systemic lymphoma or may be the only site of lymphomatous involvement. Other benign or malignant tumors that can cause proptosis include optic nerve glioma, meningioma, orbital hemangioma, sarcoma, and metastatic lesions. The most important cause of sudden and progressive proptosis in children is orbital rhabdomyosarcoma.

218. (b) False. Superior vena cava syndrome (SVCS) refers to the constellation of signs and symptoms that accompany the occlusion of the superior vena cava, either due to internal or external causes. Although it is commonly described as an oncologic emergency, it is not only nonemergent in the majority of cases but also increasingly found in patients who do not have cancer.

219. (a) Radioactivity is the term used to describe how much energy is being released by radioactive material in a given time. Radioactivity is measured in curies (Ci) in the English measurement system or the becquerel (Bq) in the SI system (SI = International System of Units or Système International). A Bq is equivalent to one disintegration of an atomic nucleus per second. A Ci is equivalent to 3.7 × 1010 disintegrations per second (dps) and is based on the decay rate of radium-226. The unit rad is often used in the English system to describe the amount of ionizing radiation that is absorbed in a cell, tissue, organ, or the body. It is equivalent to 100 ergs of energy deposited in 1 g of tissue. The gray (Gy) is equivalent to 1 J of energy deposited in 1 kg of tissue. One Gy is equivalent to 100 rad. The rem (roentgen equivalent man) is a unit of equivalent dose which is used to measure the long-term biological risk related to ionizing radiation exposure (in the United States). The sievert (Sv) is the international unit (SI) for equivalent dose. One Sv is equivalent to 100, rather than 1000, rem.

220. (b) The fluoropyrimidine derivatives, 5-Fluorouracil (5-FU), and its oral prodrug capecitabine are mainstays of oncologic therapy. The therapeutic and toxicologic effects of 5-FU and capecitabine are attributed to their deleterious incorporation into RNA and DNA and to their inhibition of thymidylate synthetase. Hand-and-foot syndrome is a characteristic adverse effect of 5-FU and capecitabine. Toxicity may result from intentional overdose, iatrogenic overdose, or therapeutic administration. A significant proportion of severe toxicity occurs in the setting of therapeutic administration rather than acute overdose and is generally attributed to genetic polymorphisms. Treatment of toxicity is largely supportive. The antidote for fluoropyrimidine toxicity is uridine triacetate, but its indications are limited, and ideally, the treating oncologist or a toxicologist should be consulted prior to its administration.

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