MD Anderson Cancer Care Series

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Oncologic Emergencies

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MD ANDERSON CANCER CARE SERIES

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Foreword

Oncologic Emergencies is a new addition to the MD Anderson Cancer Care Series. The focus of this book is on oncologic emergencies in cancer patients and survivors. The chapters are written by clinicians at our institution who have a wealth of knowledge and experience related to the medical care of acutely ill cancer patients.

For more than 70 years, our institution has been devoted to the eradication of cancer. Initially, our acutely ill cancer patients received medical care in a small ward. Over the past seven decades, our institution has grown and evolved, and we now have the largest emergency center in a comprehensive cancer center. Our emergency center is a unique facility where our patients receive treatment for a wide spectrum of emergencies. Some of the patients are acutely ill owing to conditions related to their cancer or cancer therapy. Others need medical care for comorbid conditions unrelated to their malignancies but that can be equally life-threatening. All of this care occurs in an environment where both patient safety and empathy are of great importance.

I recommend this book to anyone who is ever faced with an acutely ill cancer patient or survivor. The reader will become equipped with valuable knowledge related to the evaluation and treatment of these emergencies and in turn will be able to provide the best care possible for his or her patients.

Houston, TX, USA — Ronald A. DePinho, MD

Preface

With the advancing age of our population coupled with an increase in the incidence of cancer along with progress in cancer care, health care professionals are faced with an increasing number of emergencies in cancer patients and survivors. This new addition to the MD Anderson Cancer Care Series will hopefully be a good resource for clinicians in the emergent and urgent settings.

This book is composed of 17 chapters, each of which is devoted to a specific topic. The authors who contributed to this book are adept clinicians with extensive experience in this realm of patient care. The chapters range from cardiac and neurologic emergencies to palliative care and ethical issues. The chapters are structured to be helpful resources to busy clinicians faced with acutely ill patients. Each chapter ends with a series of key practice points along with a list of useful suggested readings.

The evaluation and treatment of oncologic emergencies is evolving into a unique discipline. Clinicians providing medical care to patients experiencing these emergencies can be faced with challenging clinical scenarios. This book will hopefully be a beneficial tool in the effort to provide the best care possible for these patients.

Houston, TX, USA — Ellen F. Manzullo, MD, FACP

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Chapter 1
Neurologic Emergencies

Patricia Brock, Katy M. Toale, and Sudhaker Tummala

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Chapter Overview

Neurologic complications of cancer and its therapy are varied and common, occurring in 30–50 % of cancer patients presenting to emergency departments or for neurologic consultations at teaching hospitals. However, a few true neurologic emergencies require rapid diagnosis and treatment to preserve neurologic function and, in some circumstances, save lives. A collaborative effort among the emergency room physician, the patient's oncologist, and consultants from neurology, neurosurgery, and radiation oncology services affords the best outcome. Even patients with advanced cancer and limited life expectancies can benefit from prompt therapy when it is appropriate for their circumstances.

Introduction

Malignant spinal cord compression, status epilepticus (SE), increased intracranial pressure (ICP), and intracerebral hemorrhage are neurologic conditions in cancer patients requiring urgent attention. This chapter details the clinical features of, possible etiologies of, diagnostic tests for, and treatment options for these complications.

Malignant Spinal Cord Compression

Malignant spinal cord compression is a grave oncologic emergency occurring in approximately 5 % of patients with terminal cancer during the last 2 years of life. It requires prompt intervention to prevent permanent paraplegia and reduced quality of life. Developments in oncologic and medical therapies have extended the life expectancy of patients with cancer, so this complication may be seen more frequently than in the past.

Metastatic spinal lesions are associated with primary breast, lung, and prostate malignancies in 60 % of cases. Renal cancer, non-Hodgkin lymphoma, and multiple myeloma each account for 5–10 % of cases. Colorectal cancer, primary cancer of unknown origin, and sarcoma account for most of the remaining cases. Men and women are affected equally. In 20 % of cancer patients, spinal cord compression is the initial manifestation of malignancy, with one third of these patients having lung cancer. The median survival duration after diagnosis of malignant spinal cord compression is only 3–6 months, and it depends on the patient's primary tumor type and ambulatory status at the time of diagnosis.

Etiology and Pathophysiologic Mechanisms

Spinal cord compression more often results from metastasis to vertebral bodies and adjacent structures than from direct metastasis to the spinal cord. These bony metastases subsequently erode into and encroach upon the spinal cord. The exact mechanism of this metastasis is not well understood. Most metastases occur in the thoracic spine owing to the bone volume or mass in this region. The clinical features of thoracic metastases are less well-defined than those of cervical or lumbosacral metastases. Also, thoracic metastases are far more dangerous than cervical or lumbosacral metastases because the blood supply in the thoracic region is vulnerable, as the width of the spinal canal relative to the width of the spinal cord is smaller than that in the other two regions. Additionally, the thoracic spine has small nerve roots that form the intercostal nerves, injury to which causes relatively innocuous symptoms. Band-like paresthesia, sometimes described as a feeling of being "squeezed, like a belt being pulled tight" or a "band of numbness about my waist," is a particularly ominous sign of epidural spinal-cord compression at the thoracic level (Fig. 1.1).

As a tumor invades the vertebral bodies, it induces activity of inflammatory mediators within the bone and soft tissue, which causes edema, venous stasis, and finally, ischemia at the level of compression. Once the tumor mass has expanded enough to cause venous congestion, an extensive inflammatory cascade ensues, causing edema of the spinal cord. If treated expediently using corticosteroids, this

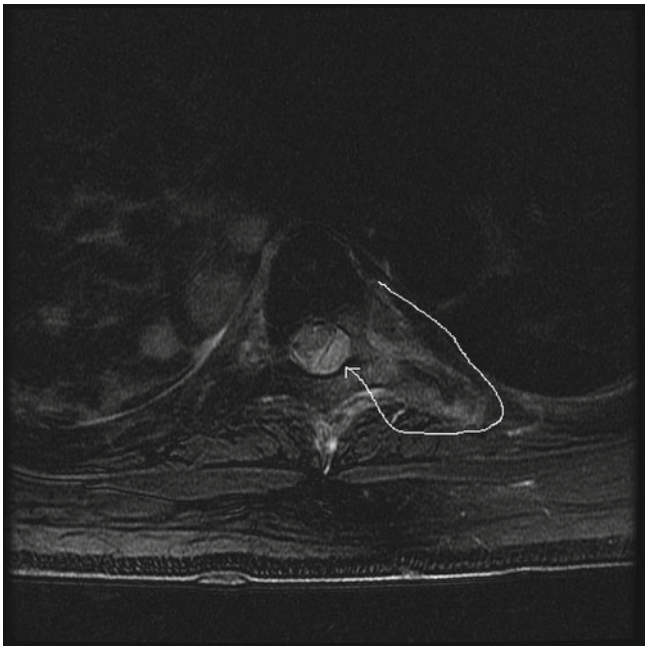

Fig. 1.1 MRI scan of the thoracic spine. At the T6 level, the epidural tumor (*outlined*) is causing impending compression of the spinal cord (*arrow*)

can be reversed. Corticosteroids are used to treat both the edema and the inflammation and, when used acutely, may ameliorate these processes. If they are left untreated, ischemia and demyelination are likely.

Cortical bone destruction in vertebral bodies does not occur until late in the disease process. The level of bone destruction must reach 30–70 % before it can be seen on plain X-rays. Bone destruction may cause a compression fracture of a vertebral body and retropulsion of bone fragments into the spinal canal, leading to mechanical compression of the spinal cord.

Clinical Manifestations and Findings

The presenting symptom of malignant spinal cord compression in about 90 % of cases is back pain. Although back pain is a common acute problem in the general population, in patients with a history of cancer, it must elicit a high degree of suspicion to ensure an early diagnosis. Pain associated with malignant spinal cord compression is often exacerbated by an axial load or associated with radicular symptoms. Pain that worsens while the patient is recumbent is unusual in those with degenerative disc disease and should raise the concern that the patient has epidural metastasis. Most often, the pain occurs at the area of vertebral compression. It is often described as gnawing or aching pain and is worse during the Valsalva maneuver. Palpation and percussion down the spine frequently help localize metastatic deposits. The pain is either unilateral or bilateral depending on the level of disease. Thoracic involvement frequently results in bilateral symptoms, whereas unilateral pain is seen with cervical or lumbosacral involvement. Complaints of thoracic pain should especially arouse suspicion, as disk herniation and spinal stenosis occur infrequently at this location. Pain while the patient is in the recumbent position worsens owing to lengthening of the spine and distension of the epidural venous plexus. Pain during motion usually is caused by vertebral body collapse and can be associated with spinal instability. Pain may precede neurologic symptoms by several weeks, so early intervention prior to the development of incontinence or inability to walk is one of the most important variables in a successful outcome aside from elimination of the primary tumor.

The second most common symptom of malignant spinal cord compression is weakness, which is present in 35–80 % of patients. Weakness is often associated with corticospinal tract signs such as hyperactive deep tendon reflexes, spasticity, and extensor plantar responses. Weakness is an ominous finding that, if not investigated, may lead to complete loss of spinal function below the level of the lesion.

Leg ataxia may be present before weakness arises and may occur without pain. Using a standardized strength scale (Table 1.1) during the initial evaluation greatly aids in monitoring the clinical course of the patient's disease. Each muscle group should be tested separately, and the results for both sides of the body should be compared. Rectal sphincter tone should be checked in all patients suspected of having malignant spinal cord compression. Patients who are immunosuppressed or

Table 1.1 Standardized muscle strength scale

Rating	Strength
0/0	No contraction
1/5	Muscle flicker, but no movement
2/5	Movement possible with gravity eliminated
3/5	Movement possible against gravity but not against resistance by the examiner
4/5	Movement possible against some resistance by the examiner
5/5	Normal strength

at risk for bleeding can be safely tested by placing a gloved finger adjacent to but not in the anal canal while the patient attempts to tighten the anal sphincter. A simple observation of the umbilicus can detect a spinal cord injury between the T10 and T12 levels. Known as the Beevor sign, this is done by having the recumbent patient flex his or her head against resistance. The umbilicus moves cephalad if the involvement is below the T10 level.

The Babinski sign is a sensitive, specific sign of corticospinal tract dysfunction, but interpretation of this valuable sign requires experience. Although most clinicians observe the great toe's movement during noxious stimulation along the lateral aspect of the bottom of the foot, the movement of the four smaller toes is a more reliable indicator. As Babinski observed, "The toes, instead of the flexing, develop an extension movement at the metatarsal joint."

Diagnosis

Diagnosis of malignant spinal cord compression begins with obtaining a thorough medical history and performing an appropriately focused physical examination coupled with a full central nervous system examination. New onset of back pain or neurologic symptoms, such as symmetric weakness and paresthesia, in a patient with known cancer should prompt further work-up for malignant spinal cord compression.

Magnetic resonance imaging (MRI) has a sensitivity rate of 93 %, specificity rate of 97 %, and overall accuracy rate of 95 % in revealing spinal cord compression. In the absence of contraindications or intolerance, MRI is usually sufficient in investigation of malignant spinal cord compression. Because one third of patients have multiple sites of compression, many researchers recommend imaging the entire spinal cord or, at minimum, the thoracic and lumbar spine. The study takes about 45 min and requires the patient to fit into an MRI scanner, lie flat, and be absolutely still.

Computed tomography (CT) myelography is a helpful technique for patients who cannot undergo MRI (e.g., those with pacemakers or extreme claustrophobia). It facilitates assessment of osseous integrity as well as the thecal sac contents and

has the added benefit of allowing for cerebrospinal fluid (CSF) sampling at the same time. Disadvantages of CT myelography include its overall greater cost than that of other available imaging tests, its invasive nature and inherent risk of contrast reaction, and postprocedure spinal tap-related headaches.

Plain X-rays, although expedient and inexpensive, are not useful in the initial evaluation of suspected malignant spinal cord compression. They are not positive for compression until nearly 70 % of the bone is destroyed, which usually occurs at a late stage in the evolution of symptoms.

Bone scanning and positron emission tomography using [^{18}F]fluoro-2-deoxy-2-d-glucose are not useful in detecting cord compression, although both do demonstrate bony metastases.

Treatment

Because malignant spinal cord compression is associated with advanced-stage cancer, all treatments of it are palliative in nature and consist of pharmacotherapy, surgery, radiotherapy (RT), or a combination of them. The goals of therapy for malignant spinal cord compression should include (1) preservation of function and mobility, (2) pain relief, (3) local tumor control, and (4) spine stability.

Corticosteroid-based therapy should be administered in cases with a suspicion of cord compression and in which myelopathy is observed. Pain, which is difficult to control in the absence of neurologic symptoms, also may be an indication for steroid use. Steroids interrupt the inflammatory cascade, leading to a reduction in vasogenic edema. Pain and neurologic symptoms often improve afterward, which can be a prognostic indicator as to how well the patient's disease may respond to therapy.

Studies of acute spinal cord injury have suggested marked neurologic improvement with the use of steroids within 8 h after injury. In a randomized controlled trial, researchers compared high-dose (100-mg loading dose, then 96 mg daily) and moderate-dose (10-mg loading dose, then 16 mg daily) dexamethasone. They found no differences in efficacy; thus, most physicians give the lower dose. Tapering of steroids is begun as soon as feasible to avoid steroid-associated complications such as hyperglycemia, insomnia, and gastrointestinal irritability. The last of these side effects is common and should be treated with antacids. A lesser known but more serious complication is lower intestinal perforation, which can be minimized by preventing the patient from becoming constipated and using the lowest possible dose of steroids. In patients presenting with undiagnosed spinal masses and no history of cancer, especially young patients, steroid use should be avoided until diagnosis. Steroids have an oncolytic effect on some tumors, particularly lymphomas and thymomas, which may delay diagnosis.

Pain may be relieved by the administration of steroids, but often, additional analgesics are required. This can be a major focus of treatment. Using the World Health

Organization's analgesic ladder, a physician can choose the most appropriate medication on the basis of the severity of the pain.

In the absence of bony instability, RT has historically been the treatment of choice for malignant spinal cord compression, preferably started within 24 h of diagnosis. This requires a prompt consultation with a radiation oncologist. Radiation is usually fractionated over a few days to weeks to minimize its harmful effects on normal tissue. Pain is often improved with RT, and further tumor growth and neurologic damage are prevented. Neurologic outcome, with the goal of ambulation following RT, depends on the patient's ambulatory status at the time of diagnosis, timing of treatment (i.e., started within 12 h after presentation), presence of a single metastatic tumor, and severity of cord compression. Patients with radiosensitive tumors, such as lymphomas, myelomas, and breast and prostate cancers, are more likely than those with less radiosensitive tumors to regain neurologic function after RT. About 90 % of ambulatory patients retain ambulation after RT alone, but less than 30 % of patients who have lost the ability to walk by the time RT is initiated regain ambulation.

Anterior vertebral body resection with stabilization may offer the best chance for a good outcome, but the procedure is a major undertaking and requires (1) a good performance status, (2) uninvolved adjacent vertebral bodies for stabilization of the spinal canal, and (3) a skilled neurosurgical team.

Emerging treatment options such as stereotactic radiosurgery and vertebroplasty may provide some symptom relief for patients who are not surgical candidates.

Summary

Malignant spinal cord compression is a neurologic emergency frequently seen in cancer patients. Even patients with advanced disease and limited life expectancy can benefit from prompt therapy when it is appropriate for their circumstances. Prompt recognition and treatment of malignant spinal cord compression by a multidisciplinary team offer the best outcomes for these patients.

Seizures in Cancer Patients

Patients with cancer have a higher incidence of seizures than that in the general population (Fidler et al. 2002). Prolonged convulsive seizures in cancer patients can lead to brain injury, rhabdomyolysis, renal failure, and death. The discussion below focuses on definitions, evaluation, etiologies, and management of prolonged seizures in adult and pediatric patients with cancer presenting to the emergency center (EC).

Definitions

Early reports on SE defined it as "whenever a seizure persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur." Many authors have defined this length of time as 30 min because experimental studies demonstrated that irreversible neuronal damage occurs after this period (Sperduto et al. 2008). However, most physicians would agree that treatment of SE should begin before 30 min elapse. Lowenstein and Alldredge (1998) proposed a revised definition of SE as "either continuous seizures lasting at least five minutes or two or more discrete seizures between which there is incomplete recovery of consciousness." This is the definition that is generally accepted today (DeAngelis and Posner 2009). This definition aims for rapid initiation of antiepileptic administration because controlling convulsive SE earlier rather than later is beneficial. Time is of the essence.

Also, a consensus on the definition of refractory SE is lacking. One suggested definition is failure of 2 or 3 anticonvulsants combined with a minimal duration of the condition of 1 or 2 h or regardless of the time elapsed since onset (Sperduto et al. 2008). Another definition is seizures lasting more than 2 h or recurring at a rate of 2 or more episodes per hour without recovery to baseline between seizures despite treatment with conventional antiepileptics (Groves 2010).

The definition of nonconvulsive SE (NCSE) is based on changes in behavior and/or mental processes from baseline that are associated with continuous epileptiform discharges on electroencephalograms (EEGs) (Groves 2010). Unfortunately, agreement regarding the duration that these alterations must be present is lacking, but most physicians would consider any abnormal epileptiform discharges on an EEG to warrant treatment.

Evaluation of a Cancer Patient with Seizures

When evaluating cancer patients with seizures, understanding the different etiologies of seizures is important. Most seizures in cancer patients are attributed to brain metastasis, but they can also be secondary to other abnormalities, such as intracranial hemorrhage and radiation necrosis. Cancers that commonly metastasize to the brain include breast and lung cancers and melanoma. Patients with primary brain tumors are also at risk for seizures. Other causes of seizures include metabolic abnormalities, infection, hypoxia, and medications that lower the seizure threshold.

Reversible posterior leukoencephalopathy syndrome can occur in cancer patients for a variety of reasons. It is associated with severe hypertension, altered mental status, and posterior cerebral T2 signals on MRI scans. Patients may present with headache, confusion, seizures, and visual impairment. Lowering the patient's blood pressure and discontinuing use of the offending agent often will prevent seizure reoccurrence. The agents most commonly associated with this syndrome include

cyclosporine, tacrolimus, sirolimus, rituximab, cytarabine, etoposide, cisplatin, oxaliplatin, gemcitabine, methotrexate, intrathecal chemotherapeutics, interferon-α, antiretroviral therapeutics, and high-dose methylprednisolone (Fidler et al. 2002).

Diagnostic Testing

Work-up for seizures should begin with a complete neurologic examination and history from a witness or family member of the patient. Laboratory values, including electrolyte, glucose, calcium, magnesium, phosphorous, and creatine kinase levels; complete blood count; and hepatic and renal function, should be obtained immediately. If indicated, arterial blood gas and antiepileptic medication levels may be measured, and echocardiograms, EEGs, and drug screens may be performed.

CT and MRI are indicated for patients with cancer who have seizures. MRI is preferred; however, CT is often performed because of its ability to quickly rule out intracranial hemorrhage. If possible, a contrast agent should be administered intravenously to help evaluate the patient for metastasis and abscesses. Lumbar punctures are indicated when an infection is suspected in the presence of fever or an elevated white blood cell count, which may be difficult to assess in cancer patients.

Management

Initial management of seizures should begin with assessing the patient's airway, breathing, and circulation. Intubation may be required if the patient has a compromised airway or severe hypoxemia. If the patient is hypoglycemic, he or she should receive 50 mL of dextrose 50 % in water. SE should be treated immediately with intravenous (IV) benzodiazepines. Studies have demonstrated lorazepam to be superior to diazepam, and pharmacokinetic studies have demonstrated that the anticonvulsant effect of lorazepam lasts much longer than that of diazepam (Groves 2010).

In addition, administration of a long-acting anticonvulsant should be started simultaneously. Phenytoin (PHT) or valproic acid is usually indicated; these two agents have the most evidence supporting their use. Unfortunately, these older generation medications may interact with chemotherapeutics and have unwanted cardiovascular side effects. This should not preclude their use given the patient's acuity and the need for controlling this unstable situation. Other agents, such as levetiracetam (LEV) and lacosamide, are frequently used, but data supporting their efficacy in patients with SE is lacking. In a recent retrospective study of 23 patients with primary or metastatic brain tumors who had SE, all of the patients were given IV PHT and LEV and oral pregabalin. SE was resolved in 70 % of the patients, with only one of the responders needing intubation. Although this study had many limitations, it provides insight into a regimen that may be safe and effective for seizures in patients with brain tumors.

LEV

Patients with primary brain tumors are unique in that they have expression of multidrug resistance proteins that may promote efflux of antiepileptic drugs from the brain. Interestingly, LEV does not appear to be a substrate for these efflux pumps (Fidler et al. 2002). In patients with brain tumors, both LEV and gabapentin are beneficial as add-on treatments of recurrent seizures and are well tolerated by most patients.

Small case series have demonstrated LEV to be effective against SE. However, only one retrospective study has compared LEV with other agents for this purpose. That study, which compared second-line treatment with PHT (70 episodes), valproic acid (59 episodes), and LEV (58 episodes) after failure of treatment with benzodiazepines, demonstrated that valproic acid was unable to control SE in 25 % of patients, PHT was unable to do so in 41 % of patients, and LEV was unable to do so in 48 % of patients. Of note, the researchers in this study did not report the incidence of cancer in the patient population.

Lacosamide

Several case reports and case series documented that administration of lacosamide led to termination of seizures after several other therapies failed. However, many reports did not include the number of patients who did not have responses to lacosamide. The dosing in these trials varied widely from 100- to 400-mg IV boluses followed by 50–200 mg twice daily. Until more data are available, lacosamide should be reserved for patients who experience failure of more traditional therapies.

Alternative Routes of Administration

The IV route is preferred for the management of SE. If IV access cannot be obtained, intramuscular (IM) midazolam should be considered. Diazepam is poorly absorbed when administered intramuscularly, so its use should be avoided. In a recent study looking at control of SE in a prehospital setting, the researchers compared IM midazolam with IV lorazepam in children and adults. Patients who weighed more than 40 kg received 10 mg of IM midazolam or 4 mg of IV lorazepam, whereas those who weighed 13–40 kg received 5 mg of IM midazolam or 2 mg of IV lorazepam. The results demonstrated that seizures were absent without rescue therapy in 73 % of the midazolam group and 63 % of the lorazepam group. Therefore, IM midazolam is at least as safe and effective as IV lorazepam. In addition to benzodiazepines, fosphenytoin may be administered intramuscularly.

For patients with contraindications to IM administration (e.g., thrombocytopenia), meta-analyses have demonstrated that buccal midazolam is superior to rectal diazepam for treatment of SE in children and young adults. Buccal midazolam is

administered by squirting the IV formulation (1 mg/mL) onto the buccal mucosa in doses of 0.5 mg/kg or a 10-mg flat dose. If a patient is unable to tolerate buccal administration, intranasal administration can be considered. Midazolam can be administered intranasally (0.1–0.4 mg/kg) using a mucosal atomization device.

NCSE

For patients in a prolonged coma state following a seizure, EEGs should be performed to assess them for NCSE. Other clinical manifestations of seizures include blank staring; periorbital, facial, or limb myoclonus; and eye-movement abnormalities such as nystagmus and eye deviation. Patients may have rambling speech or be mute. A waxing and waning state alternating between agitation and obtundation can occur. Inappropriate laughing, crying, or even singing may occur. In a study of patients with cancer and altered mental status, 6 % of the patients had NCSE with no previous evidence of brain metastasis. Authors have also reported NCSE in patients with primary brain tumors. In non-cancer patients, the mortality rate for NCSE has been reported to be 18 %, but the rates in cancer patients are unknown. The gold standard for treating and confirming NCSE is clinical and EEG improvement following benzodiazepine administration. Treatment with 1–4 mg of IV lorazepam is given in incremental steps depending on the overall patient situation. Like in patients with SE, follow-up with administration of a long-acting IV antiepileptic agent (LEV, lacosamide, PHT, or valproic acid) is needed. Figure 1.2 shows an EEG of a patient with NCSE treated with lorazepam.

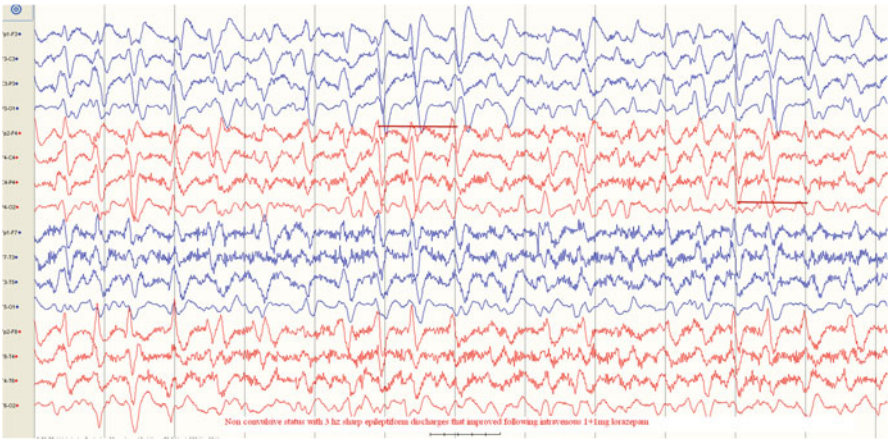

Fig. 1.2 EEG of a patient with NCSE treated with lorazepam

Refractory SE

Agents used for treatment of refractory SE include midazolam, propofol, high-dose thiopental, phenobarbital, pentobarbital, topiramate, tiagabine, ketamine, isoflurane, and lidocaine. Propofol is used most often because it is more effective and safer than the other agents.

Conclusion

SE is an emergency medical condition in patients with cancer. New therapies for it have emerged that are less toxic than previous therapies and have few or no drug interactions. Although data on these therapies are lacking, they have been effective in small case series. Prompt treatment and cessation of seizure activity in cancer patients are imperative to prevent long-term complications of seizures.

Space-Occupying Lesions

Brain Metastasis

Systemic cancer-related brain metastases are up to 10 times more common than primary malignant brain tumors. Metastatic lesions can affect the skull or several intracranial sites. Even though skull metastases are more common, intracranial metastases are more likely to be symptomatic in the involved structures (cerebral hemisphere, brain stem, pituitary gland, choroid, and meninges). Skull metastases may invade the epidural space and compress the brain from outside or involve the cranial nerves as they exit the skull. Intracranial metastasis can be the initial presentation in a small number of patients with no known cancer. Brain metastasis can also be asymptomatic (e.g., 11 % of patients with newly diagnosed lung cancer).

The estimated incidence of brain metastasis is 150,000–200,000 cases per year. The frequency of this metastasis is increasing owing to increased survival durations resulting from effective systemic treatment, improved imaging modalities, and the aging population. Common tumors of origin for brain metastases are lung cancer, breast cancer, and melanoma; others include renal cell carcinoma, colon cancer, and gynecologic malignancies. About 10 % of patients with metastatic brain lesions present with intraparenchymal hemorrhage, and the most common primary cancers associated with it are melanoma, renal cell carcinoma, thyroid cancer, and choriocarcinoma. Brain metastases from unknown primary tumors are well recognized, and the primary site may not be discovered, even at autopsy.

Clinical signs and symptoms of brain metastases result from destruction or displacement of normal brain tissue by growing lesions and associated edema.

Increased ICP and vascular injury may also ensue. Urgent evaluation in the EC is warranted for patients presenting with symptoms of new brain metastases or decompensation owing to known brain metastases. Acute management issues in the EC are related to control of medical problems resulting from these metastases (cerebral edema, elevated ICP, seizure, headache, nausea/vomiting, and control of coagulopathy). Requesting timely, appropriate consults (e.g., neurology, neurosurgery, radiation oncology) is warranted for patients with brain metastases.

Diagnostic Work-Up

Neuroimaging studies for brain metastases include brain CT and MRI. CT without contrast is useful for quick assessment of patients whose condition rapidly deteriorates. CT can identify hemorrhages, large brain lesions, and herniation. In less urgent situations or when other diagnostic modalities are being considered (for ischemic stroke, paraneoplastic conditions, or an infectious process), MRI with and without contrast should be performed. Use of CT or MRI without contrast may result in misidentification of tumors as strokes. Contrast enhancement is also important for detection and grading of tumors. For patients with persistent alteration of consciousness despite initial therapy or incomplete mental status improvement following a clinical seizure, EEGs are required to rule out subclinical electrographic seizure activity. Furthermore, electrolyte and glucose measurement, complete blood counts, coagulation profiling, and liver and renal function tests should be performed.

Clinical Presentation

Most patients present with brain metastasis after establishment of a diagnosis of primary cancer, often within 2 years. Five percent to ten percent of patients present with both systemic and intracranial disease at the time of initial diagnosis. Brain metastases may develop with overt symptoms or remain clinically silent.

Any patient with a history of cancer in whom new neurologic symptoms develop warrants careful examination. Common clinical presentations of brain metastases include headache, seizures, and focal neurologic deficits (focal weakness, focal sensory complaints, and cranial neuropathy). Signs and symptoms are generally insidious over a period of weeks to months. Occasionally, neurologic deficits have an acute onset secondary to vascular compromise. This may result from general hypercoagulability, disturbance of arterial flow, tumor embolization, or hemorrhage into the lesion. Tumor-related headaches are nonspecific, often resembling other types of headache and not necessarily accompanied by papilledema. The rare Foster Kennedy syndrome is a meningioma or plasmacytoma compressing the optic nerve, resulting in ipsilateral optic atrophy and papilledema in the contralateral eye. EC

policy should be that any new headache in a cancer patient requires work-up. Neurologic signs and symptoms of a brain metastasis can be progressive, reflecting local expansion and growth of the tumor. Vigilance for relatively uncommon sites of metastases, such as the pituitary gland, is important. Breast cancer is the most common tumor that spreads to the pituitary gland. Clinical symptoms of pituitary gland metastases include ocular palsies, hypopituitarism, bitemporal hemianopia, alteration in consciousness varying from confusion to coma, and severe headache should rare pituitary apoplexy occur. Recognition and treatment of diabetes insipidus and panhypopituitarism and neurosurgical consultation for pituitary apoplexy are urgently needed.

Location-Related Symptoms

By being aware of the following symptoms, a physician can match them with brain masses at specific locations. (1) A dominant frontal lobe mass may manifest with expressive speech difficulty. Frontal lobe syndrome symptoms can vary, including loss of vitality, slow thinking, odd behavior, inappropriate remarks, irritability, trouble with executive planning that can be covered up by euphoria, platitudes in speech, and robotic behavior. Of note, a large frontal lobe mass (nondominant) can be clinically silent or accompanied by symptoms similar to those described above. (2) A dominant temporal lobe mass may cause receptive speech difficulty, depression, and/or apathy. A nondominant temporal lobe mass may manifest with visual field deficits and inability to recognize daily familiar sounds, such as a loud clap. A dominant parietal lobe mass may impair arithmetic skills and cause right-left confusion and inability to copy 3-dimensional constructions. (3) A nondominant parietal lobe mass may result in neglect owing to the patient being unaware of his or her deficits. (4) Occipital lobe masses cause visual field deficits, cortical blindness, and trouble identifying colors.

Differential Diagnosis

A clinical history along with MRI may establish the diagnosis of brain metastasis, although biopsy is warranted at times. A brain lesion is not necessarily a tumor. In one study, 6 of 54 patients with known cancers and single brain lesions did not have metastasis according to biopsy; 3 patients did not even have neoplastic lesions. Other diagnostic entities include intracerebral hemorrhage, brain abscesses, viral infections, cerebral radiation necrosis, paraneoplastic syndromes, and brain demyelination (tumefactive multiple sclerosis). Cerebral radiation necrosis occurs most often after stereotactic radiosurgery rather than whole-brain RT. MRI may demonstrate a “Swiss cheese/soap bubble” appearance with spreading wavefront margins.

Cerebral Edema and Elevated ICP

Cerebral edema is a potentially devastating complication of brain metastasis. The two main types of cerebral edema are (1) vasogenic edema, which is increased fluid in the extracellular space, and (2) cytotoxic edema, which is increased cellular fluid. Brain tumors cause vasogenic edema. Potentiating factors that worsen tumor-associated edema are seizures, use of chemotherapeutic agents (e.g., interleukin-2), and RT. Radiation necrosis following stereotactic radiosurgery can mimic brain tumors, with accompanying cerebral edema. Cerebral edema can be focal (from a lesion) or diffuse (hepatic postanoxic-ischemic swelling). Brain edema is predominantly cleared through the CSF. Brain edema displaces brain tissue, impairs consciousness, and causes buckling of and irreversible damage to the brain stem.

The mainstay of treatment of cerebral edema is corticosteroid use, as it is effective in reducing perilesional edema resulting from brain metastasis or a primary brain tumor. General dosing recommendations are 10 mg of dexamethasone in an IV bolus followed by 4–6 mg of IV dexamethasone every 6–12 h depending on the patient's clinical status. Use of corticosteroids improves CSF dynamics, predominantly, the outflow over the convexity.

If cerebral edema results in elevated ICP, reducing the ICP to maintain adequate cerebral blood flow is imperative. Interventions can include mechanical ventilation with a partial pressure of arterial carbon dioxide goal of 35–40 mm Hg and partial pressure of arterial oxygen goal of 80–120 mm Hg, maintenance of euvolemia, prevention of hypotension, maintenance of appropriate sedation and analgesia, elevation of the head end of the patient's bed to 30°, and CSF drainage. Use of osmotic diuretics should be considered in combination with these interventions. Options for this include mannitol (initial dose of 1 g/kg) and hypertonic saline (3.0–23.4 %), the doses of which can be titrated to a serum osmolality of 320 mOsmol/L or serum sodium concentration of 145–155 mmol/L. Administration of hypertonic saline requires using a central line. Three percent saline has an osmolality similar to that of 20 % mannitol. A single bolus of 250 mL of 3 % saline or 30 mL of 23.4 % saline can be given. Mannitol may induce hypovolemia and renal failure. Both agents have been associated with acute heart failure, pulmonary edema, and rebound increases in ICP. Two recent meta-analyses demonstrated hypertonic saline to be superior to mannitol in decreasing ICP; however, they demonstrated no clear benefit in neurologic outcome.

The efficacy of acute hyperventilation is lost after 6 h. Also, hypocapnia (partial pressure of arterial carbon dioxide less than 25 mm Hg) may induce severe cerebral vasoconstriction, causing ischemia.

CSF diversion (via ventriculostomy, sometimes urgent at bedside) is warranted for management of hydrocephalus, particularly in patients with intraventricular or pineal region tumors. A ventriculostomy tube is connected to a manometric CSF drainage system draining at 10–15 cm of water. If the CSF is bloody, drainage at no more than 0 cm of water should be considered to reduce clotting in the catheter.

If the patient already has an Ommaya reservoir, tapping of the reservoir can be considered after careful evaluation of the patient's neuroimages and measurement of the opening pressure. Lumbar puncture is contraindicated in patients with significant cerebral edema, hydrocephalus, or frank or impending herniation.

Urgent craniotomy and tumor debulking can be considered when the measures described above are unsuccessful and aggressive management is considered to be warranted (e.g., unknown tumor for diagnosis, relatively controlled primary tumor status, single large metastases, resectable lesions, potentially reversible situations [hemorrhage]).

Cerebral Herniation Patterns

Cerebral edema increases the size of a brain tumor and symptoms related to displacement of the thalamus as well as lateral, upward, and downward displacement of the brain stem, all of which can have major consequences.

Cingulate herniation occurs when the cingulate gyrus in the frontal lobe herniates under the falx and compresses both frontal lobes, leading to urinary incontinence and bilateral extensor plantar responses. The ipsilateral anterior cerebral artery may be compressed, causing frontal lobe ischemia.

Temporal lobe (uncal) herniation at the tentorium cerebelli causes ipsilateral III cranial nerve compression with the resulting sudden appearance of wide pupils with loss of light reflex. Lateral displacement of the brain stem with compression of pyramidal long tracts against the tentorial edge results in ipsilateral hemiparesis. As herniation progresses with further brain stem buckling, the pupils contract, which may be falsely mistaken as improvement of the patient's condition.

Central herniation occurs when a medially located mass forces the thalamus-midbrain through the tentorial opening (central displacement). This causes shearing of the penetrating basilar artery branches with irreversible brain stem damage. Central displacement results in poorly responsive midposition pupils, Cheyne-Stokes breathing, extensor or flexor posturing, and loss of oculocephalic reflexes.

Posterior fossa lesions can be displaced upward with pupillary and eye-movement abnormalities accompanied by significant changes in consciousness level. Downward displacement of these lesions (tonsillar herniation through the foramen magnum) can compress the brain stem and cause apnea. This is why patients with cerebellar metastases may present with cough and syncope.

Intracranial Hemorrhage

Certain tumor types (melanoma, renal cell carcinoma, thyroid carcinoma, and choriocarcinoma) are known to be associated with spontaneous hemorrhage. Intracerebral hemorrhage (subdural, epidural, or subarachnoid) can occur in cancer

patients, with thrombocytopenia as a risk factor for it. Subdural metastases may exude fluid into the subdural space, with a resulting subdural hematoma or effusion.

Prompt evaluation and management of intracranial hemorrhage in the EC are critical. Neurosurgical consultation should be performed immediately. Supportive measures such as blood pressure control, correction of coagulopathy, and management of elevated ICP may improve outcomes.

Blood Pressure Management

A recent study demonstrated that interventions such as rapid lowering of blood pressure (systolic blood pressure goal, 140 mm Hg) can reduce hematoma growth in patients with intracerebral hemorrhage (Delcourt and Anderson 2012). One agent recommended for blood pressure management is labetalol because of its ability to preserve cerebral blood flow and its minimal effect on ICP. Labetalol should be administered in a 10- to 20-mg IV bolus followed by infusion at 2–8 mg a minute. Another option is nicardipine owing to its ability to improve cerebral perfusion pressure and lack of effect on ICP. Nicardipine administration should be started as a continuous infusion at a rate of 5 mg an hour and titrated to a maximum dose of 15 mg an hour. Nicardipine may be preferred over labetalol for its quick onset of action and short half-life.

Correction of Coagulopathy

Platelet transfusion is warranted if the patient is thrombocytopenic. Depending on the clinical situation, other treatments to be considered include fresh frozen plasma (2 U), vitamin K (5–10 mg IV), protamine sulfate (1 mg per 100 U of heparin), prothrombin complex concentrate (25–50 U/kg), and recombinant factor VIIa.

Central Nervous System Infections

Antibiotics are recommended if a brain abscess or meningitis is part of the initial differential diagnosis of a brain lesion. In nonimmunocompromised patients, coverage with cefotaxime, metronidazole, and vancomycin is recommended. Immunocompromised patients, transplant recipients, and hematologic cancer patients may need broader coverage for fungal (amphotericin), parasitic (toxopyrimethamine, sulfadiazine, leucovorin), and/or atypical bacterial ([*Nocardia* species] imipenem) infections. An in-depth review of central nervous system infections is outside the scope of this chapter.

Conclusion

Neurologic complications of cancer are common and result in devastating consequences if not managed early. In collaboration with specialized neurology services, emergency room physicians can act quickly to prevent further deterioration and permanent neurologic sequelae.

Key Practice Points

- Neurologic events, including malignant spinal cord compression, SE, cerebral edema, and intracranial hemorrhage, are true emergency conditions in patients with cancer, and prompt treatment of them is imperative to prevent long-term complications.
- The complaint of back pain in a patient with cancer should elicit a high degree of suspicion of spinal cord compression.
- Prolonged convulsive seizures in cancer patients can lead to brain injury, rhabdomyolysis, renal failure, and death.
- Lung cancer, breast cancer, and melanoma are the most common tumors of origin for brain metastases.
- Incomplete mental status improvement following a clinical seizure necessitates an EEG.
- Administration of 10 mg of IV decadron is the mainstay of initial treatment of cerebral edema and suspected malignant spinal cord compression.

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Chapter 2
Metabolic and Endocrine Oncologic Emergencies

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Contents

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Chapter Overview

Homeostatic regulation of key metabolites in cancer patients is often dysfunctional or perturbed by the malignancy or its treatment. Cancer and its treatment can also perturb the endocrine systems that regulate organ functions and metabolism. Deficiencies and excesses in electrolytes, metabolites, and hormones are discussed

from the practical standpoint of acute clinical management in this chapter. Common etiologies and treatment approaches are also presented.

Introduction

Cancer and its treatment can lead to endocrine and metabolic dysfunction. Oncologists and emergency physicians should be vigilant in checking for these endocrine and metabolic sequelae so that prompt, appropriate treatment can be given to improve the patient's quality of life and avoid serious morbidity or mortality. Syndrome of inappropriate antidiuretic hormone secretion and tumor lysis syndrome are covered elsewhere in the Nephro-Urologic Emergencies in Patients with Cancer chapter and thus are not discussed in this chapter.

Hyponatremia

The human body contains about 60 % water, and the sodium/water balance (i.e., intake and loss of sodium relative to intake and loss of water) is regulated by the renin-angiotensin system, atrial natriuretic peptides, and the osmoregulation centers in the brain and antidiuretic hormone. Hyponatremia (sodium level less than 135 mEq/dL) is a common abnormality in cancer patients that may indicate serious underlying disease. It is associated with adverse prognosis for cancer.

Clinical Manifestations

Hyponatremia has a nonspecific clinical presentation that ranges from no symptoms to multiple neurologic symptoms of headache, behavioral changes, lethargy, confusion, seizure, stupor, and even coma. The severity of symptoms depends on the rate of decline and degree of hypo-osmolality. Severe hyponatremia can cause seizures, permanent brain damage, brain stem herniation, respiratory failure, and death.

Approach

Hyponatremia is often recognized via laboratory measurement of plasma electrolytes. Hypotonicity must be confirmed by measuring osmolality. Hyponatremia with normal osmolality (pseudohyponatremia) can be a laboratory artifact caused by hyperlipidemia (corrected sodium level = sodium level + 0.2 × triglyceride level [mg/L]) or hyperproteinemia (corrected sodium level = sodium level + 0.025 × protein

[if protein level is greater than 8 g/dL]). Extreme hyperglycemia (corrected sodium level = sodium level + [glucose level − 5]/3.5) and administration of hypertonic mannitol result in hypertonic hyponatremia by shifting intracellular water to the extracellular fluid, diluting the plasma sodium concentration. Identifying the causes of hyponatremia requires additional laboratory evaluations, including urinary sodium measurement, thyroid and adrenal function tests, and correlation with clinical history. Hypovolemic hyponatremia owing to gastrointestinal and renal salt loss is common in cancer patients. Hypervolemic hyponatremia also is often seen in patients with severe liver cirrhosis, fluid third-spacing, or congestive heart failure.

Treatment

Treatment of hyponatremia involves rebalancing the total body water and sodium levels using the following means (usually in combination):

- Decreased free water intake
  - Fluid restriction to 500–800 mL of free water per day if not hypovolemic.
- Increased free water excretion
  - Treatment with demeclocycline at the usual dose range of 600–1200 mg a day produces a reversible form of nephrogenic diabetes insipidus (DI), inhibiting antidiuretic hormone-induced cyclic adenosine monophosphate formation.
  - Treatment with loop diuretics such as furosemide may be added in nonhypovolemic patients to enhance free water clearance.
  - Vaptans can be used to block V2 receptors and promote free water excretion (aquaresis). Their action peaks within a few hours and generally subsides after 12–24 h, and they are efficacious for hypervolemic hyponatremia.
- Increased sodium intake
  - Oral salt intake: sodium chloride tablets.
  - Parenteral salt intake: normal saline (0.9 % NaCl) or hypertonic saline (3 % NaCl) at a rate of 1 mL/kg/h.
- Decreased sodium loss
  - Fludrocortisone: 0.1–0.6 mg a day orally.
- Treatment of the underlying etiology of hyponatremia

Hypernatremia

Hypernatremia (sodium level greater than 145 mEq/L) is always accompanied by a hyperosmolar state and cellular dehydration. Hypernatremia results from excess sodium intake, excess renal reabsorption of sodium, reduced water intake, or

increased water loss. Hypernatremia is seen in about 1 % of hospitalized patients, and young, old, and chronically ill patients are vulnerable to it.

Clinical Manifestations

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 acute increase in the level of sodium. Thirst is the first symptom unless the patient has hypodipsia owing to hypothalamic dysfunction. Other symptoms include restlessness, weakness, and lethargy that may progress to coma. Muscle weakness and central nervous system changes are usually not manifested until the sodium level is greater than 160 mEq/L. DI is characterized by polyuria, urine hypo-osmolality, and compensatory polydipsia. If water loss exceeds water intake, intravascular volume depletion and hypernatremia will ensue.

Approach

Central DI is most frequently caused by events that affect the anterior pituitary or related hypothalamic nuclei (e.g., surgery, destruction by tumors, hemorrhage, head injury, infarction, infection).

Most cases of familial/congenital nephrogenic DI are caused by V2 receptor mutations and aquaporin-2 water channel mutations. However, these causes are rare in cancer patients. Acquired nephrogenic DI can result from the nephrotoxicity of drugs. Common nephrogenic DI-inducing drugs are lithium, foscarnet, and clozapine. Although distal tubular defects develop in about half of patients given ifosfamide, nephrogenic DI leading to hypernatremia is uncommon in them.

In cancer patients, inadequate water intake can have many causes, including obstruction of the gastrointestinal tract, chemotherapy-induced nausea and vomiting, and chemotherapy- or radiotherapy-induced mucositis. Primary hypodipsia can result from dysfunction of the thirst center in the supraoptic nucleus of the hypothalamus owing to a primary or metastatic malignancy (e.g., breast cancer, lung cancer) or treatment of a central nervous system tumor using surgical resection and/or radiation. Reasons for increased water loss include diuretic use, high fever, burn, or diarrhea. Iatrogenic causes of hypernatremia include inappropriate intravenous fluid administration, total parenteral nutrition, and hemodialysis. Drugs that decrease the effect of antidiuretic hormone include demeclocycline, lithium, amphotericin, vinblastine, glyburide, propoxyphene, colchicine, acetohexamide, tolazamide, and methoxyflurane.

A water deprivation test may differentiate between central and nephrogenic DI. A serum uric acid level greater than 5 mg/dL in a polyuric polydipsic patient is highly suggestive of central DI.

Treatment

Administration of free water

- Give water enterally or intravenously with solutions low in electrolytes (i.e., dextrose 5 % in water, 0.2 % NaCl). Total body water deficit can be estimated by 0.6 weight (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 less than 2 mEq/L/h until the symptoms resolve. The remaining water deficit can be corrected in 48 h.
- Patients with hypodipsia should receive a prescribed amount of water per day on a regular basis.
- Central DI usually is treated with desmopressin (DDAVP) at a typical dose of 5–20 μg intranasally every 12 h, 1–2 μg subcutaneously once a day, and 0.1–0.2 mg orally twice a day.
- A low-salt diet along with use of thiazide diuretics that induce natriuresis is the treatment of choice for nephrogenic DI. Indomethacin has been used to treat drug-induced nephrogenic DI.
- Discontinue treatment with any drugs that may contribute to nephrogenic DI (e.g., lithium) if clinically appropriate.

Hypokalemia

Hypokalemia (potassium level less than 3.5 mEq/L) is perhaps the most common electrolyte abnormality in cancer patients.

Clinical Manifestations

Patients with mild hypokalemia (3.0–3.5 mEq/L) usually are asymptomatic. In those with severe hypokalemia (less than 3 mEq/L), symptoms may range from mild to severe and are potentially fatal. Cardiac manifestations may range from flat T waves, T-wave depression, and prominent U waves to serious arrhythmias. Neurologic manifestations include muscle weakness, paresthesia, and paralysis.

Approach

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, from the skin during profuse sweating

or owing to severe burns, and from the kidneys as a result of intrinsic tubular defects, type 1 renal tubular acidosis, or drug-related effects. Common examples of potassium-wasting drugs are loop diuretics, aminoglycosides, cyclophosphamide, ifosfamide, carboplatin, cisplatin, and amphotericin B. Hypokalemia owing to excess mineralocorticoid activity may result from pharmacologic administration of corticosteroids or ectopic Cushing syndrome, which is associated with some cancers. Alkalosis, either respiratory or, on a larger scale, metabolic, may precipitate hypokalemia via a transcellular potassium shift. Drugs that cause potassium redistribution include insulin, vitamin B_{12}, β-adrenergic agonists, theophylline, and chloroquine.

Hypokalemia is diagnosed via potassium measurement. Medications used and dietary history are helpful in determining 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 diagnose renal potassium loss.

Treatment

Replace potassium according to the following guidelines (Fig. 2.1):

- The oral route is preferred over other routes if feasible.
- The intravenous route may be used in patients with profound hypokalemia or unable to tolerate oral replacement. The rate of intravenous administration should not exceed 20 mEq/h diluted in intravenous fluid through a peripheral vein. The infusion rate may be as high as 40 mEq/h 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.
- About 40–50 % of patients with hypokalemia also have hypomagnesemia, which must be corrected to fully correct the potassium-depleted state.
- Potassium-sparing diuretics, such as amiloride and spironolactone, inhibit potassium excretion and may have a role in decreasing renal potassium wasting.

POTASSIUM

Serum potassium 3.3 - 3.5 mEq/L give:		
☐	**Oral** Access	**Potassium CHLORIDE 40 mEq** PO tablet (do not crush) ____ times one dose
☐	**CVC/PICC** Access	**Potassium CHLORIDE 40 mEq** in 100 mL of sterile water (premixed bag) IVPB over 2 hours
☐	**Peripheral** Access	**Potassium CHLORIDE 50 mEq** in 1000 mL of 0.45% sodium chloride IVPB over 5 hours ***(Notify Physician if patient fluid restricted)*
Serum potassium less than 3.3 mEq/L give:		
☐	**Oral** Access	**Potassium CHLORIDE 80 mEq** PO tablet (do not crush) ____ times one dose
☐	**CVC/PICC** Access	**Potassium CHLORIDE 40 mEq** in 100 mL of sterile water (premixed bag) IVPB over 2 hours per dose for **2 doses (Total 80 mEq over 4 hours)**
☐	**Peripheral** Access	**Potassium CHLORIDE 50 mEq** in 1000 mL of 0.45% sodium chloride IVPB over 5 hours ***(Notify Physician if patient fluid restricted)*

Fig. 2.1 Preprinted orders for potassium replacement

Hyperkalemia

Hyperkalemia is also a common electrolyte disorder in cancer patients.

Clinical Manifestations

Severe clinical manifestations of hyperkalemia usually are absent until the serum potassium level is greater than 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. At greater than 7.5 mEq/L, nonspecific symptoms such as muscle weakness, cramping, and paralysis of different muscle groups may occur.

Hyperkalemia causes depolarization of excitable membranes. This membrane depolarization leads to the excitability of nerves and muscles, causing cramps, muscle weakness, and paralysis. The most vital organ with excitable membranes is the heart. Specific electrocardiogram (EKG) changes and potentially fatal arrhythmias may be present, but the serum potassium level is not correlated directly with a particular EKG pattern. An early EKG abnormality associated with hyperkalemia is peak T waves followed by a progressive QRS widening to a "sinusoidal" wave. Ventricular tachycardia, fibrillation, and asystole may occur.

Approach

Inappropriate potassium content in intravenous fluid and total parenteral nutrition are common iatrogenic causes of hyperkalemia. A significant release of intracellular potassium will cause hyperkalemia, as in the case of tumor lysis syndrome. Insulin deficiency, β-blocker therapy, and acidemia can elevate serum potassium levels.

Drug-induced hyperkalemia most often occurs in patients with impaired renal excretion of potassium. The drugs commonly used by cancer patients that may cause hyperkalemia include cyclosporin A, tacrolimus, heparin, mitomycin C, and pentamidine.

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.

Treatment

Treatment of hyperkalemia depends on its severity and rate of development.

- If possible, discontinue medications that may contribute to hyperkalemia, such as β-adrenergic blockers, nonsteroidal anti-inflammatory drugs,

angiotensin-converting enzyme inhibitors, potassium supplements, and others described above.
- Monitor EKG continuously if the potassium level is greater than 6 mEq/L.
- For EKG changes, infuse intravenously (usually for less than 60 min):
  - Calcium (1–2 g of calcium gluconate or 0.5–1.0 g of chloride)
  - Sodium bicarbonate
  - Glucose (usually 25 g) plus 6–8 U of regular insulin
  - β-adrenergic agonists, which promote potassium entry into cells
- Increasing the renal excretion of potassium can be attempted with the use of loop diuretics.
- Removal of potassium from the body should be attempted with the use of 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.
- Emergent hemodialysis may be used in refractory cases.

Hypocalcemia

In hospitalized cancer patients, the hypocalcemia rate is about 13.4 %. Hypocalcemia may affect the proper functioning of many intracellular and extracellular processes, such as muscle contraction, nerve conduction, and blood coagulation.

Clinical Manifestations

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, congestive heart failure, and cardiac arrest. Chronic hypocalcemia with hypoparathyroidism causes extrapyramidal disorders, cataracts, and skin and hair changes. Vitamin D deficiency causes rickets and osteomalacia in patients with hypocalcemia.

Approach

In most cancer patients, the etiology of hypocalcemia is obvious. Excluding a decreased serum calcium level owing to low albumin and serum protein levels, the major causes of hypocalcemia are hypoparathyroidism and hypomagnesemia.

Hypocalcemia may be a feature of tumor lysis syndrome. Severe osteoblastic bone metastases (especially from prostate carcinoma) are often associated with hypocalcemia. The toxicity of certain chemotherapeutic agents (e.g., platinum compounds) also may lead to hypocalcemia.

Evaluation of hypocalcemia involves confirmation of it by measuring the ionized calcium level. If the cause of hypocalcemia is not clear, laboratory analysis of intact parathyroid hormone (PTH), magnesium, phosphate, 25-hydroxy vitamin D3, 1,25-dihydroxy vitamin D3, creatinine, and 24-hour urinary calcium levels is helpful.

Treatment

Treatment of hypocalcemia depends on its severity and cause.

- Severe hypocalcemia is treated parenterally with intravenous calcium chloride (0.5–1.0 g) or gluconate (1–2 g) over 5–10 min. Calcium gluconate is preferred over other agents because it is less likely to cause tissue necrosis if extravasated.
- Hypomagnesemia is a common cause of hypocalcemia. Concurrent hypomagnesemia should be treated with intravenous 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 must receive lifelong supplementation of calcium and vitamin D. Vitamin D supplements can be given in 1-hydroxylated form or as calcitriol. Calcitriol is preferred for patients with renal insufficiency or failure because of decreased 1-α-hydroxylase levels in the kidneys.
- Attention should be paid to phosphate binding.

Hypercalcemia

Hypercalcemia of malignancy is observed in 10–15 % of cancer patients. It is a poor prognostic sign that is associated with short survival durations.

Clinical Manifestation

Patients with mild hypercalcemia (calcium level less than 12 mg/dL) usually have no symptoms, whereas those with moderate or severe hypercalcemia are frequently symptomatic. 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. Musculoskeletal symptoms are myalgia, arthralgia, and weakness.

Approach

Hypercalcemia may result from increased bone resorption, renal tubular reabsorption, and gastrointestinal absorption of calcium. In cancer patients, hypercalcemia of malignancy accounts for more than 90 % of hypercalcemia cases. Hypercalcemia in cancer patients may have different pathophysiologic mechanisms. The most common humoral factor secreted by tumors causing hypercalcemia is PTH-related peptide. In general, patients with PTH-related peptide-induced hypercalcemia have advanced malignant disease and poor prognoses. Other humoral factors, such as interleukin-1 and -6, prostaglandins, and tumor necrosis factor, can mediate hypercalcemia in cancer patients. Extensive lytic bone metastasis, particularly in patients with breast cancer or multiple myeloma, may lead to hypercalcemia. Increased levels of 1,25-dihydroxy vitamin D_3 may mediate hypercalcemia in patients with Hodgkin disease or non-Hodgkin lymphoma.

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). However, accurate measurement of the ionized calcium level confirms 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.

Treatment

Treatment of hypercalcemia should be aimed at lowering serum calcium levels and correcting its underlying causes, if possible.

- Primary hyperparathyroidism can be cured via parathyroidectomy.
- Use of medications (e.g., calcium-containing medications, thiazide diuretics) that contribute to hypercalcemia should be discontinued.
- The initial and first-line treatment of hypercalcemia is hydration with crystalloid intravenous fluid. In patients with overall fluid overload, use of a loop diuretic would be helpful.
- Bisphosphonates (etidronate, clodronate, pamidronate, zoledronate, and ibandronate) inhibit bone resorption by osteoclasts. Zoledronate (4–6 mg intravenously over 30 min) is more widely used than pamidronate (60–90 mg intravenously over 4–24 h).

- Second-line agents include calcitonin (salmon calcitonin 4 IU/kg subcutaneously every 12 h). Calcitonin has a rapid onset of action, although its effectiveness may decrease within 2–3 days.
- Other less widely used agents include glucocorticoids, plicamycin (25 μg/kg intravenously), and gallium nitrate (200 mg/m^2 intravenously).

Hypomagnesemia

The incidence rate of the common electrolyte deficiency hypomagnesemia in hospitalized cancer patients has been as high as 17.1 %. 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 would indicate depletion of total body magnesium.

Clinical Manifestations

Magnesium is a major cation in the body, and only 1–2 % of total body magnesium is present in the extracellular space. It 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.

Approach

In cancer patients, hypomagnesemia is a very common abnormality that is related to low intake and impairment of renal reabsorption or intestinal absorption of magnesium. It is also related to prolonged intravenous feeding, nasogastric suction, chronic alcoholism, intestinal malabsorption, and diarrhea. The renal toxicity of chemotherapy (e.g., platinum-based drugs, cyclophosphamide, ifosfamide) and anti-infective medications (e.g., amphotericin, aminoglycosides) also influences hypomagnesemia.

Hypomagnesemia is often associated with other electrolyte abnormalities, such as hypokalemia and hypocalcemia. Concurrent measurement of other electrolytes, such as calcium, phosphate, and potassium, should be considered.

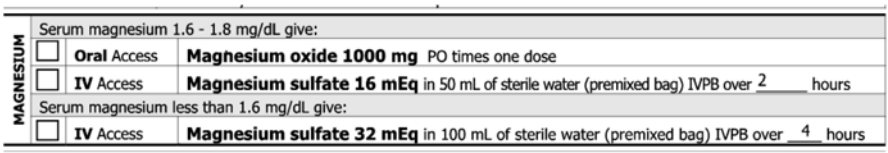

Fig. 2.2 Preprinted orders for magnesium replacement

Treatment

Magnesium replacement is indicated in cancer patients when the serum magnesium level is repeatedly below normal (Fig. 2.2).

1. Oral replacement is preferred over parenteral when feasible. However, diarrhea may be a dose-limiting side effect.
2. When intravenous 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.

Hypermagnesemia

Hypermagnesemia is uncommon. It is usually caused by increased intake of magnesium in the presence of renal insufficiency or iatrogenic factors.

Clinical Manifestations

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. Respiratory depression, coma, and complete heart block may occur at levels greater than 9 mg/dL. Asystole and cardiac arrest can occur at levels greater than 10 mg/dL.

Approach

The major causes of hypermagnesemia are renal failure and excessive ingestion of magnesium-containing medications in the presence of renal insufficiency. 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. Overreplacement of magnesium in intravenous fluid or with hyperalimentation also can cause hypermagnesemia. A less common cause in cancer patients is tumor lysis syndrome.

Excessive magnesium intake usually is evident in the patient's dietary and medication history. Hypermagnesemia is diagnosed via direct measurement of serum magnesium levels. Renal function should be assessed by measuring blood urea nitrogen and creatinine levels.

Treatment

- Discontinuation of magnesium intake is the first step.
- Patients with mild symptoms and normal renal function can simply be observed to ensure that the magnesium level returns to normal.
- Magnesium excretion can be accelerated by hydration with crystalloid fluid and a loop diuretic given intravenously.
- In cases of severe hypermagnesemia (particularly with hypotension and/or cardiac arrhythmia), calcium should be administered intravenously to reverse respiratory depression, hypotension, and cardiac arrhythmia.
- Emergent dialysis should be considered for patients with life-threatening hypermagnesemia.

Hypophosphatemia

Hypophosphatemia is quite prevalent, as it is found in about 2–3 % of all hospitalized patients and about 30 % of cancer patients.

Clinical Manifestations

Acute severe hypophosphatemia may lead to generalized neurologic findings such as lethargy, confusion, disorientation, and 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 less than 0.8 mg/dL. Cardiac muscle also can be affected by severe hypophosphatemia, and 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. Hypophosphatemic rickets can result from ifosfamide nephrotoxicity. Osteomalacia, waddling gait, bone tenderness, pseudofractures, and fractures can occur in patients with chronic hypophosphatemia.

Approach

Acute hypophosphatemia occurs primarily in hospitalized patients with serious illnesses and pre-existing phosphate depletion. Acute severe hypophosphatemia usually results from translocation of phosphate into cells. Respiratory alkalosis, intravenous glucose administration (including hyperalimentation), gram-negative sepsis, and insulin therapy can induce transcellular shift of phosphate.

Chronic hypophosphatemia results from an elevated PTH or PTH-related protein level, consumption of oral phosphate binders, accelerated bone formation, increased humoral factors suppressing renal reabsorption of phosphate, or intrinsic renal tubular defect in phosphate reabsorption.

Tumor-induced (oncogenic) osteomalacia is a rare syndrome characterized by hypophosphatemia, excessive urinary phosphate loss, reduced 1,25-dihydroxy vitamin D concentrations, and osteomalacia. Tumor secretion of fibroblast growth factor 23 may be responsible for renal phosphate wasting.

Rapid cancer or normal cell proliferation in ill patients with nutritional deprivation or catabolism may cause hypophosphatemia. Chronic hypophosphatemia together with hypocalcemia occasionally is associated with extensive osteoblastic metastasis of prostate, breast, lung, and other malignancies. Patients with rapidly progressing leukemia or lymphoma (e.g., Burkitt lymphoma) may have hypophosphatemia. As with the use of granulocyte colony-stimulating factors, hematopoietic reconstitution after stem cell transplantation or stem cell harvesting in preparation for transplantation also cause hypophosphatemia.

The liver plays a significant role in phosphate homeostasis. In a retrospective study, postoperative serum phosphate levels dropped in all 44 patients who underwent right or extended right hepatic lobectomy. Authors have reported hypophosphatemia in a patient with hepatocellular carcinoma complicating liver cirrhosis. Hypophosphatemia in malnourished patients (especially alcoholics) results from a combination of magnesium deficiency, vitamin D deficiency, and malabsorption. Refeeding of high-calorie diets in severely malnourished patients can lead to refeeding syndrome with hypophosphatemia.

Intrinsic renal tubular defects in phosphate reabsorption may occur in patients with Fanconi syndrome, myeloma, or amyloidosis. Hypophosphatemia also may be associated with the use of chemotherapeutic drugs such as platinum compounds and alkylating agents (e.g., ifosfamide).

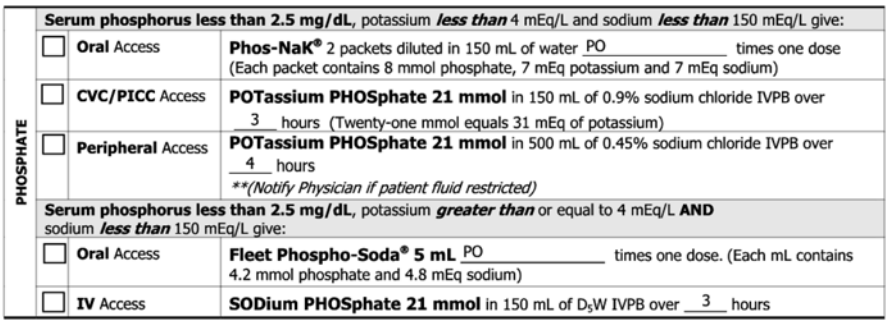

Fig. 2.3 Preprinted orders for phosphate replacement

Hypophosphatemia is demonstrated via measurement of the serum phosphate level. Measurement of renal function and potassium, magnesium, calcium, vitamin D metabolite, and PTH levels is helpful in determining 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.

Treatment

Significant hypophosphatemia (phosphate level less than 2 mg/dL), especially in the context of underlying phosphate depletion, should be corrected promptly (Fig. 2.3).

- Phosphate can be safely administered intravenously at an initial dose of 0.2–0.8 mmol/kg over 6 h (i.e., 10–50 mmol over 6 h). Higher doses (1.5–3.0 mmol/kg over 12 h) 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.
- In patients with oncogenic osteomalacia, complete resection of the tumor will reverse all biochemical abnormalities. If cure is not possible, reversal of 1,25-dihydroxy vitamin D deficiency via calcitriol administration and correction of hypophosphatemia are effective palliative therapies.

Hyperphosphatemia

Hyperphosphatemia is found in 2.5 % of cancer patients.

Clinical Manifestations

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.

Approach

In the absence of renal failure, the fasting serum phosphate level is determined primarily according to the renal tubular reabsorption rate. A massive amount of phosphate can be released into the extracellular fluid via extensive cellular breakdown. Extensive rhabdomyolysis and hemolysis may cause hyperphosphatemia in the same way.

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. Excess phosphate intake (including use of phosphate-containing laxatives) is another potential cause of hyperphosphatemia.

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 in the detection and management of hyperphosphatemia owing to cellular breakdown.

Treatment

The emergency treatment of hyperphosphatemia involves supportive care and treatment of symptomatic hypocalcemia.

- 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.
- Dietary restriction of phosphorus, although an important factor in the control of the serum phosphorus level in the chronic setting, poses practical problems that limit its success in most patients.

- Aluminum-containing antacids are used to inhibit phosphorus absorption in the gastrointestinal tract, but accumulation of aluminum has serious long-term toxic effects in patients with impaired renal function. Calcium-based phosphate binders have largely replaced aluminum compounds. However, excessive amounts of absorbed calcium present a different problem. Use of nonabsorbable phosphate binders that are aluminum- and calcium-free (800–1600 mg of sevelamer with each meal) can prevent these issues.

Hyperglycemia

Diabetes mellitus is a common disease, and a large number of cancer patients have co-existing diabetes. Glucocorticoids are used frequently in cancer patients for various conditions, and steroid-induced diabetes mellitus is common. Because diabetes mellitus is an extensive subject, this section focuses on the acute complications of it in cancer patients.

Clinical Manifestations

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.

Approach

The serum glucose level is regulated by absorption, cellular uptake, gluconeogenesis, and glycogenolysis, which are regulated by the pancreas, intestines, liver, kidneys, and muscle. Hyperglycemia can result from perturbation of the hormones involved in glucose regulation, such as insulin and glucagon, and from dysfunction of the organs involved in glucose homeostasis.

Diabetic ketoacidosis is decompensated catabolism triggered by a relative or absolute deficiency in insulin secretion. A deficiency in insulin relative to the glucagon level inhibits glycolysis and increases glycogenolysis and gluconeogenesis in the liver. Malonyl coenzyme A levels decrease because of inhibited acetyl coenzyme A carboxylase and glycolysis. As a result, fatty acid oxidation and ketone body formation increase. The pathophysiology of hyperosmolar hyperglycemic nonketotic

coma is similar to that of diabetic ketoacidosis except that ketone bodies are not formed and extremely high glucose levels result from diminished urine output.

Glucocorticoid administration (in combination therapy regimens and for edema in patients with brain metastasis, prevention of transplant rejection, graft-versus-host disease, and nausea with vomiting) is the most common cause of diabetes mellitus. Treatment with interleukin-2, interferon-α, interferon-γ, streptozocin, homoharringtonine, or L-asparaginase may result in diabetes. Patients who receive allogeneic stem cell transplants are likely to receive both glucocorticoids and tacrolimus and are particularly at risk for hyperglycemia.

Drugs such as ifosfamide and mercaptopurine can damage the renal tubules and cause glycosuria and Fanconi syndrome. A false-positive reaction with the testing agent for urinary ketones can be caused by treatment with mesna (2-mercaptoethane sulfonate sodium).

A random glucose level greater than 200 mg/dL or a fasting plasma glucose level greater than 126 mg/dL on more than one occasion can indicate diabetes mellitus. A glucose tolerance test (2-hour oral glucose tolerance test: glucose level of at least 200 mg/dL) usually is not necessary except in borderline cases. Glycosylated hemoglobin (hemoglobin A1C) reflects the level of glucose in the preceding 1.5 months.

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 patients with hyperosmolar hyperglycemic nonketotic coma, the plasma glucose level may be well over 800 mg/dL, and the serum osmolality may be more than 100 mOsm higher than normal. Mild ketosis may be present because of starvation, but ketoacidosis will not be present. In severe cases, when volume depletion causes circulatory collapse, 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 (Table 2.1).

Treatment

Management of the blood glucose level depends on the severity of the blood glucose abnormality and on the underlying pathophysiologic mechanism of the increase in the level. In general, oral agents are less likely to be effective than other types of agents in patients who are deficient in insulin.

Table 2.1 Precipitating factors for diabetic ketoacidosis and hyperosmolar hyperglycemic nonketotic coma

Trauma
Burns
Dialysis
Hyperalimentation
Cushing syndrome and other endocrinopathies
Hemorrhage
Myocardial infarction
Renal disease
Subdural hematoma
Cerebrovascular accident
Infection/sepsis
Antimetabolites
L-asparaginase
Diazoxide
Didanosine
Glucocorticoids
Immunosuppressives (tacrolimus, cyclosporin A)

Table 2.2 Treatment of diabetic ketoacidosis in the emergency room

First hour (may very often take place in an emergency center)
1. Intravenous normal saline at 15 mL/kg/h
2. Regular insulin: 10- to 20-U intravenous bolus followed by continuous infusion at 0.1 U/kg/h; monitor glucose level hourly at bedside
3. EKG: look for evidence of myocardial infarction as a precipitating factor and peaked T or U waves as signs of severe abnormality in potassium level
4. Arterial blood gases: confirm metabolic acidosis; if pH is less than 7.0, consider administration of a small amount of sodium bicarbonate (about 1 mEq/kg)
5. Look for precipitating factors
Second hour
1. Continue intravenous infusion of normal saline at 15 mL/kg/h
2. Regular insulin: continue insulin drip; if glucose level is less than 250 mg/dL, change intravenous fluid to D5NS, but if glucose level does not decrease, double the insulin infusion rate

Treatment of diabetic ketoacidosis or hyperosmolar hyperglycemic coma focuses on supplemental insulin, rehydration, correction of electrolyte abnormalities and severe acidosis, and identification of the precipitating factors (particularly important to rule out sepsis) (Table 2.2).

- Hydrate with intravenous crystalloid fluid.
- Regular insulin usually is given as an intravenous bolus of 0.1 U/kg followed by a maintenance intravenous infusion of 0.1 U/kg/h. The amount of insulin required for treatment of hyperosmolar hyperglycemic coma may be less than that required for diabetic ketoacidosis.

Hypoglycemia

Hypoglycemia is defined as a blood glucose level less than 50 mg/dL. The timing of symptoms relative to a fasting or postprandial state can distinguish among various etiologies.

Clinical Manifestations

A progressive pattern of responses to hypoglycemia is determined by the availability of glucose to the brain. 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, are prevalent. When the glucose level is less than 50 mg/dL, neuroglycopenic symptoms of blurry vision, slurred speech, confusion, and difficulty with mental concentration appear. When the glucose level is less than 40 mg/dL, the patient may become drowsy, confused, or combative. A further prolonged decrease below 30 mg/dL can cause seizures, permanent neurologic deficits, and death.

Approach

Glucagon and epinephrine are the two major counterregulatory hormones. Other hormones that respond to hypoglycemia are norepinephrine, cortisol, and growth hormone, but their effects are delayed. Glucagon and epinephrine immediately stimulate hepatic glycogenolysis followed by gluconeogenesis. Primary adrenal insufficiency and primary hypothyroidism and hypopituitarism are associated with hypoglycemia (Table 2.3). 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.

In many cancer patients, hypoglycemia is associated with cancer-related malnutrition and fat and muscle wasting, which impair gluconeogenesis. Non-islet cell tumors can secrete hormones such as insulin-like growth factor (IGF)-2, which, by binding to insulin receptors, causes hypoglycemia. Excessive glucose consumption by large tumors also may cause hypoglycemia.

For diabetic cancer patients receiving sulfonylurea or insulin, the most common cause of hypoglycemia may be delayed or decreased food intake. Cancer patients who receive irradiation of the head and neck area, have metastatic or primary tumors, or undergo treatment affecting the hypothalamic-pituitary area are at risk for hypopituitarism.

Table 2.3 Precipitating factors for hypoglycemia in cancer patients

Hypoadrenalism
Overaggressive treatment of acute hyperglycemia
Inadequate caloric intake
Recent change in dose or type of insulin or oral hypoglycemic agent
Ethanol intoxication
Factitious hypoglycemia
Hepatic impairment
Sepsis
Worsening renal insufficiency
Malfunctioning, improperly adjusted, or incorrectly used insulin pump
Massive tumor bulk or humoral paraneoplastic syndromes
Drugs (insulin secretagogues, insulin, β-blockers, salicylates, pentamidine, phenylbutazone, antibacterial sulfonamides)

Simultaneous measurement of fasting blood glucose, insulin, and C-peptide levels is helpful in investigating the cause of hypoglycemia. Hypoglycemia with an inappropriately elevated level of insulin suggests autonomous insulin secretion and factitious use of insulin (normal or decreased C-peptide level) or insulin secretagogues (increased C-peptide level). When hypoglycemia occurs with a correspondingly decreased level of insulin, non-insulin-mediated causes of fasting hypoglycemia must be explored. The normal insulin-to-fasting plasma glucose ratio is less than 0.33. This ratio is increased in patients with insulinoma.

A 72-h fast with measurement of glucose and insulin levels every 6 h can be used to diagnose hypoglycemia in most patients with insulinomas. Measurement of the C-peptide level helps distinguish between endogenous insulin secretion and exogenous insulin. The IGF-2 level and IGF-2:IGF-1 ratio are useful in screening patients with IGF-2-producing non-islet cell tumor-induced hypoglycemia.

Treatment

- 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 intravenously) or glucose (50 mL of 50 % dextrose in water intravenously) 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 and glucagon may be administered to raise the blood glucose level.
- Treatment of postprandial hypoglycemia is primarily dietary. The diet should have a low carbohydrate content. Use of α-glucosidase inhibitors (acarbose or miglitol) may be helpful.

Adrenal Crisis

The adrenal gland is a site of hematogenous metastasis exceeded in frequency by the lungs, the liver, and bone. Despite the high prevalence of adrenal metastasis, clinically evident primary adrenal insufficiency is seen infrequently. The hypothalamic-pituitary area may be damaged by a tumor or its treatment (irradiation or surgery), leading to secondary adrenal insufficiency. However, the most frequent cause of adrenal insufficiency in cancer patients is suppression of the hypothalamic-adrenocortical axis by chronic/repeated exposure to corticosteroids.

Clinical Manifestations

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.

Cachexia, weakness, and electrolyte abnormalities can be easily explained by poor intake, malnutrition, chemotherapy side effects, or paraneoplastic syndromes. Adrenal insufficiency may develop gradually and have a variety of causes not often observed in cancer patients (Table 2.4). Inadequate production of glucocorticoids to meet the metabolic requirements of the body leads to potentially life-threatening adrenal crisis.

Approach

Cancer patients at increased risk for primary adrenal insufficiency are those with loss of adrenal function owing to use of medications that inhibit glucocorticoid synthesis or bilateral adrenal resection, metastasis, infection, or hemorrhage. Etomidate, a commonly used intravenous anesthetic, may inhibit cortisol synthesis, but short-term use of it as in rapid-sequence intubation does not cause any problems. At high doses, imidazoles, ketoconazole, fluconazole, and itraconazole inhibit cytochrome P450-dependent enzymes in glucocorticoid synthesis. Other drugs used in cancer patients that may inhibit glucocorticoid synthesis include aminoglutethimide, megestrol, and mitotane. Many cancer patients are immunocompromised, particularly those with leukemia or lymphoma or who have undergone stem cell

Table 2.4 Precipitating factors for adrenal insufficiency

Surgery
Anesthesia
Volume loss, acute hemorrhage
Trauma
Asthma
Hypothermia
Alcohol intoxication
Myocardial infarction
Sepsis
Hypoglycemia
Pain
Psychotic breakdown
Depressive illness
Drugs
Imidazoles
Etomidate
Mitotane
Megestrol
Metyrapone
Aminoglutethimide
Morphine
Reserpine
Chlorpromazine
Barbiturates

transplantation. In these patients, infection of both adrenal glands with cytomegalovirus, mycobacteria, or fungi may lead to adrenal insufficiency. Adrenal insufficiency also may occur as a result of bilateral adrenal hemorrhage owing to coagulopathy and thrombocytopenia or bilateral adrenalectomy (e.g., renal cell carcinoma with bilateral adrenal metastasis treated with radical nephrectomy and contralateral adrenalectomy). Treatment with the anti-cytotoxic T-lymphocyte antigen-4 antibody ipilimumab disrupts immunotolerance of cancer cells, but autoimmune hypophysitis may occur in up to 17 % of cancer cases. Early screening for and treatment of hypopituitarism is recommended for all patients given ipilimumab.

Cancer patients at increased risk for secondary adrenal insufficiency are those with a history of irradiation of the hypothalamic-pituitary area, prolonged or repeated treatment with glucocorticoids, or surgical intervention for pituitary tumors or craniopharyngiomas. Metastasis to the hypothalamic-pituitary region is uncommon, and endocrine sequelae are rare. Pituitary apoplexy is an acute life-threatening event characterized by severe headache and circulatory collapse caused by intrapituitary hemorrhage. An expanding hemorrhagic mass may compress parasellar structures, including cranial nerves.

The cortisol level is measured primarily using plasma specimens to assess adrenal function. About 20–30 % of patients with bilateral adrenal metastasis will experience adrenal insufficiency, which occurs when more than 80 % of adrenal tissue is

lost. Screening tests include basal 8:00 a.m. serum cortisol measurement, dynamic testing with 1 μg of cosyntropin or metyrapone (30 mg/kg given orally overnight), and insulin tolerance testing (insulin-induced hypoglycemia).

Treatment

If a cancer patient presents to an emergency center in a state of 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, especially if the patient has an increased risk of adrenal insufficiency as described above.

- In the event of severe stress or illness (circulatory instability, sepsis, emergency surgery, or other major complications), hydrocortisone at 300 mg a day or other glucocorticoids at equipotent doses may be administered intravenously in divided doses.
- Fludrocortisone (9-α-fluor-hydrocortisone, 0.05–0.20 mg/day) may replace mineralocorticoids.
- Correction of hypovolemia with an intravenous bolus of normal saline or other crystalloid fluid such as lactated Ringer's solution may require use of up to 3 L in the first 8 h.
- Treatment of hypoglycemia should be immediate if the patient is symptomatic. Dextrose 50 % in water (50–100 mL) may be given via intravenous push and should be followed by D5W administration. If intravenous access is not quickly available, glucagon (2 mg) may be given subcutaneously or intramuscularly, but the effect may be delayed by about 10–20 min.

Hypothyroidism

The prevalence of hypothyroidism is 2–3 % in the general population, particularly in women (female:male ratio, 10:1). Therefore, female cancer patients with pre-existing or co-existing hypothyroidism are common. Moreover, hypothyroidism may arise as a complication of cancer or its treatment.

Clinical Manifestations

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.

Approach

In cancer patients, irradiation is an important cause of hypothyroidism (primary, secondary, or tertiary). In these patients and long-term cancer survivors, a history of radiotherapy should raise suspicion for hypothyroidism. The radiation exposure threshold for the development of hypothyroidism is about 10 Gy. Neck irradiation, which is administered for a variety of head and neck tumors and lymphoma, is associated with a high incidence of primary hypothyroidism.

Thyroid dysfunction resulting from use of cytotoxic chemotherapeutic agents is uncommon except for L-asparaginase. In addition to blocking thyroid-binding globulin synthesis, L-asparaginase may reversibly inhibit thyroid-stimulating hormone (TSH) synthesis and lead to temporary hypothyroidism. Treatment with bexarotene (Targretin), a retinoid X receptor-selective ligand, causes secondary hypothyroidism in a dose-dependent manner. Cytokine therapy with interferons and interleukins is also associated with hypothyroidism and transient thyroiditis with eventual hypothyroidism. Hypothyroidism secondary to metastatic infiltration and replacement of the thyroid by cancer is extremely rare.

The diagnosis of hypothyroidism is confirmed using thyroid function tests. In most cases, TSH and free T4 testing is adequate for initial evaluation.

In patients with myxedema coma, serum thyroid hormone levels are usually 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. Myxedema coma occurs most often in elderly hypothyroidism patients with superimposed precipitating events (Table 2.5).

Table 2.5 Factors that may precipitate myxedema coma

Exposure to cold temperature
Infection (usually pneumonia)
Congestive heart failure
Trauma
Drugs (phenobarbital, narcotics, anesthetics, benzodiazepines, lithium, and iodides)
Cerebrovascular accident
Hemorrhage (especially gastrointestinal)

Recognition of hypothyroidism may be difficult in the emergency care setting. Thyroid function test results typically are not available within 24 h. 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.

Treatment

Once hypothyroidism (frank or subclinical) is diagnosed, the patient should receive thyroid hormone replacement therapy.

Management of myxedema coma in the critical care setting has been reviewed. Rapid clinical diagnosis with early therapy may be life-saving. Treatment may be emergent and is usually given prior to laboratory confirmation. In critically ill patients, if myxedema coma is highly suspected, 0.5 mg of levothyroxine should be given intravenously followed by 0.025–0.100 mg a day. Other supportive measures, such as correction of hypothermia using slow rewarming and ventilatory and circulatory support, are critical.

Thyrotoxicosis

Although less common than hypothyroidism, thyrotoxicosis is still a common disease, with a prevalence of 20–25 per 100,000 in the general population. Like hypothyroidism, more female than male patients have thyrotoxicosis, with a female:male ratio of 5:1. Therefore, female cancer patients commonly have pre-existing or co-existing hyperthyroidism. Moreover, thyrotoxicosis may arise as a complication of cancer or its treatment.

Clinical Manifestations

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 Graves ophthalmopathy, exophthalmos, extraocular muscle palsies, lid lag, and upper lid retraction. Neuropsychiatric symptoms of agitation, anxiety, restlessness, fear, paranoia, and mood swings are observed as well as depressed mental function, which may range from a placid demeanor to frank confusion. Neuromuscular symptoms include fine tremor in the hands, proximal myopathy (common in the elderly), thyrotoxic hypokalemic paralysis (mostly in Asians), and acute thyrotoxic polyneuropathy. Gastrointestinal symptoms include hyperphagia, diarrhea, nausea, vomiting, and abdominal pain.

Dermatologic symptoms include flushed skin, moist arms, fine and straight hair, alopecia, and pretibial myxedema. Apathetic hyperthyroidism is seen primarily in the elderly, and congestive heart failure, atrial fibrillation, and weight loss are prominent features.

Approach

Thyrotoxicosis can result from unregulated release of thyroid hormones and thyroglobulins. This may be caused by direct injury to the thyroid gland, destructive infiltrative processes, or autoimmune-mediated destruction of thyroid follicular cells.

Hyperthyroidism can result from unregulated or stimulated synthesis, release of thyroid hormones, and growth of thyroid tissues. Toxic goiters and adenomas and thyroid carcinomas are examples of unregulated autonomous thyroid tissue. Inappropriate stimuli for hyperfunction of the thyroid may be TSH, human chorionic gonadotropin, thyroid-stimulating immunoglobulins, and TSH receptor mutations, or it may arise from faulty intracellular signal transduction mechanisms.

Large quantities of iodide are present in many drugs (e.g., approximately 9 mg of iodine in a 300-mg dose of amiodarone), antiseptics (e.g., povidone-iodine), and contrast media used in radiology. Iodine-induced hyperthyroidism usually occurs in patients with underlying thyroid diseases.

Thyrotoxicosis can result from autoimmune thyroiditis precipitated by bioimmunotherapy for cancer with cytokines. In addition to the mechanism of excess iodide described above, amiodarone induces thyroiditis. Radiation-induced painless thyrotoxic thyroiditis occurs infrequently after external beam irradiation of the neck.

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.

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. When the serum human chorionic gonadotropin level rises above 200 IU/mL, hyperthyroidism is likely.

Thyroid storm, an acute decompensation of severe or untreated thyrotoxicosis, is a life-threatening complication with a high mortality rate. Precipitating factors for thyroid storm are listed in Table 2.6.

Thyrotoxicosis is diagnosed by measuring thyroid hormone (thyroxin and triiodothyronine) and TSH levels. Pituitary and hypothalamic causes of thyrotoxicosis

Table 2.6 Precipitating factors for thyroid storm

Infection
Iodine therapy
Contrast radiographic studies
Premature withdrawal of antithyroid therapy
Pulmonary embolism
Visceral infarction
Ingestion of thyroid hormone
Surgery
Trauma
Severe emotional stress
Hypoglycemia
Diabetic ketoacidosis
Hyperosmolar nonketotic coma

are unusual. Measurement of free thyroid hormones instead of total serum hormone prevents changes introduced by variations in thyroxine-binding globulin. A radioiodine 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, history of irradiation of the neck or chest area) or tumors that may secrete human chorionic gonadotropin. Burch and Wartofsky proposed a set of diagnostic criteria (e.g., fever, tachycardia, tachyarrhythmia, mental status change) and scoring system for thyroid storm.

Treatment

Treatment of Graves disease includes antithyroid 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. The management of severe thyrotoxicosis or thyroid storm consists of treatments directed at inhibition of thyroid hormone synthesis, blockade of thyroid hormone release, inhibition of thyroxine-to-triiodothyronine conversion, support for systemic decompensation, and correction of precipitating factors. Rapid inhibition of thyroid hormone synthesis with thionamide drugs followed within hours by blockade of the release of preformed thyroid hormone by iodides is the cornerstone of acute management.

Thionamides function as antithyroid drugs primarily by preventing synthesis of thyroid hormones. The half-life of thyroxine (T4) is 7 days in euthyroid individuals but somewhat shorter in thyrotoxic patients. This accounts for the several-week delay in onset of clinical improvement in most patients. Doses range from 100 to

600 mg/day for propylthiouracil and from 10 to 60 mg/day for methimazole. Gastrostomy or jejunostomy tubes and rectal administration of propylthiouracil or methimazole can be used in patients who cannot receive medications orally or nasogastrically.

β-blockers, both cardioselective and noncardioselective, are important adjuncts in treating hyperthyroidism. β-blockade provides rapid relief of hyperadrenergic symptoms and signs of thyrotoxicosis, such as palpitations, tremors, anxiety, heat intolerance, and various eyelid signs, before any decrease in thyroid hormone level. β-blockers are useful in preventing hypokalemic periodic paralysis in susceptible individuals, and they are the drugs of choice for thyroiditis, which is self-limiting. High doses of propranolol (greater then 160 mg/day) also can inhibit peripheral conversion of T4 to T3.

Saturated solution potassium iodide (3–5 drops) is administered orally every 8 h to block release of thyroid hormones in patients with thyrotoxicosis. At pharmacologic concentrations (100 times the normal plasma level), iodides decrease thyroid gland activity. This action involves decreasing thyroid iodide uptake, iodide oxidation, and organification and blocking the release of thyroid hormones (Wolff-Chaikoff effect). Iodide has substantial benefits in treating thyroid storm. However, administration of iodide may be problematic in thyrotoxic patients with severe dysfunction of the upper gastrointestinal tract. Rectal delivery of potassium iodide is an effective alternative to parenteral sodium iodide in severely thyrotoxic patients with small bowel obstructions.

The oral contrast agents ipodate and iopanoic acid 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 intravenous 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.

The enterohepatic circulation of thyroid hormones is higher in patients with thyrotoxicosis than in individuals without it. Bile-salt sequestrants bind thyroid hormones and thereby increase their fecal excretion. Colestipol has been an effective, well-tolerated adjunctive agent in the treatment of hyperthyroidism.

Other treatment options include corticosteroids (e.g., dexamethasone, which inhibits peripheral thyroxine conversion), lithium, amiodarone, and potassium perchlorate. Plasmapheresis and hemoperfusion are effective ways to remove excess thyroid hormone. Emergent thyroidectomy is hazardous in the presence of severe thyrotoxicosis, and radioactive iodine does not offer rapid control of thyroid function.

Carcinoid Crisis

Carcinoid tumors secrete a variety of polypeptides, biogenic amines, and prostaglandins, which cause a constellation of symptoms collectively known as carcinoid syndrome. Severe, life-threatening manifestations are known as carcinoid crisis.

Clinical Manifestations

Carcinoid syndrome includes the following symptoms: skin flushing, telangiectasia, cyanosis, diarrhea, intestinal cramping, bronchoconstriction, and valvular heart disease. In many patients, the primary complaints are severe flushing, nausea, and faintness. In a crisis situation, seizure, hypotension, severe bronchoconstriction, and cardiopulmonary arrest can occur.

Approach

Provocation of 5-hydroxytryptamine and release of other humoral mediators in patients with carcinoid crisis may be mediated by the release of catecholamines from the adrenals, which activates adrenergic receptors on tumor cells. Somatostatin receptors on the tumor cells primarily have an inhibitory effect.

Typically, cancer patients presenting with symptoms of carcinoid crisis already have diagnoses of carcinoid tumors. Typical carcinoid syndrome is associated most often with midgut carcinoid tumors. Ninety percent of patients with carcinoid syndrome have metastatic disease. Carcinoid crisis can be precipitated by chemotherapy and invasive procedures such as fine-needle biopsy and laser bronchoscopy.

Treatment

Symptomatic treatments of carcinoid crisis usually target bronchoconstriction, flushing, and diarrhea.

- Octreotide acetate, a somatostatin analog, is effective in controlling and markedly reducing the symptoms of carcinoid crisis. Dose escalation up to 5950 μg a day has been reported.
- Both hypertensive and hypotensive carcinoid crises respond to treatment with octreotide, and octreotide and lanreotide should be considered for prophylactic and emergency use in all patients with carcinoid syndrome prior to and during anesthesia, surgery, biopsy, and chemoembolization of liver lesions.
- Supportive measures include oxygen, intubation, and ventilator support (if necessary) and intravenous crystalloid fluid administration.
- Octreotide, dexamethasone, and H1 and H2 blockers should be administered quickly.
- Mild bronchoconstriction may respond to inhaled anticholinergic and/or β-adrenergic agonists and theophylline.
- Cyproheptadine can block 5-hydroxytryptamine receptors and may be helpful in controlling symptoms caused by 5-hydroxytryptamine.
- Catecholamine administration should be avoided.

Key Practice Points

- Treatment of hyponatremia is best tailored after identifying the etiology.
- Use of vaptans for hyponatremia increases aquaresis by binding to V2 receptors in the kidney.
- Acute severe symptomatic forms of hyponatremia should be treated with hypertonic saline with the caution that fast correction of hyponatremia can lead to osmotic demyelinating syndrome.
- Thirst is the first line of defense against hypernatremia except in patients with hypodipsia.
- Differential diagnosis of hypernatremia: central versus nephrogenic DI, and administer treatment based on etiology.
- Oral replacement of potassium is preferred over other routes of replacement.
- The rate of intravenous potassium replacement must be regulated carefully. Potassium chloride must be appropriately diluted in intravenous fluid. The infusion rate may be as high as 40 mEq/h through a central venous catheter.
- Treat or prevent cardiac arrhythmia in hyperkalemic patients.
- Pharmacologically induce transmembrane shift of potassium into cells in patients with hyperkalemia.
- Remove potassium from the body of a hyperkalemic patient by enhancing renal excretion or administering Kayexalate or dialysis.
- Treat hypocalcemia with calcium preparations and vitamin D.
- Pay attention to magnesium and phosphate levels in patients with hypocalcemia.
- Primary hyperparathyroidism and malignancy account for more than 90 % of hypercalcemia cases.
- Hypercalcemia of malignancy is associated with poor prognosis.
- First-line treatments of hypercalcemia of malignancy include intravenous hydration with crystalloid fluids and bisphosphonate infusions.
- Calcitonin is a useful second-line therapeutic for hypercalcemia of malignancy.
- Magnesium deficiency is very common in cancer patients, who must be screened and monitored for it.
- Diligent correction of hypomagnesemia is recommended.
- Hypermagnesemia is usually iatrogenic in the presence of renal insufficiency.
- Use pharmacologic preparations containing magnesium with caution in the presence of renal insufficiency.
- Treatment of hypermagnesemia involves removal of magnesium. In severe cases, calcium is given intravenously to antagonize the effect of magnesium on the neuromuscular and cardiovascular systems.
- Acute severe hypophosphatemia usually results from a transmembrane shift of phosphate into cells in the setting of respiratory alkalosis, intravenous glucose administration (including hyperalimentation), gram-negative sepsis, or high-dose insulin therapy.
- Oncogenic osteomalacia is rare but causes severe hypophosphatemia and phosphate renal wasting.

- In patients with phosphate abnormalities, the calcium level must be monitored in addition to the phosphate level.
- Treatment of hyperphosphatemia with nonabsorbable phosphate binders that are aluminum- and calcium-free (800–1600 mg of sevelamer with each meal) is preferred over other treatments.
- Diabetic ketoacidosis is diagnosed according to the triad of metabolic acidosis, hyperglycemia, and presence of ketone bodies in the urine or blood.
- Sepsis and serious infections must be ruled out as the precipitating events for diabetic ketoacidosis and hyperosmolar hyperglycemic coma, especially in immunocompromised cancer patients.
- Treatment of hyperglycemia primarily involves intravenous administration of fluids and insulin.
- Severe hypoglycemia with change in mental status can be promptly treated with glucagon (1–2 mg subcutaneously or intravenously) or glucose (50 mL of 50 % dextrose in water intravenously).
- Mild hypoglycemia (glucose level of 50–60 mg/dL) can be treated with simple carbohydrate intake.
- Non-islet cell tumor-induced hypoglycemia is treated with glucose infusion, glucocorticoids, or glucagon and tumor debulking.
- A screening test for adrenal insufficiency is basal 8:00 a.m. serum cortisol measurement.
- Dynamic testing using high- and low-dose cosyntropin, metyrapone (30 mg/kg given orally overnight), and insulin tolerance testing (insulin-induced hypoglycemia) can be used to diagnose primary and secondary adrenal insufficiency.
- In patients with adrenal insufficiency (suspected or confirmed) and severe stress (circulatory instability, sepsis, emergency surgery, or other major complications), hydrocortisone at 300 mg a day or other glucocorticoids at equipotent doses may be administered intravenously in divided doses.
- Myxedema coma is rare but life-threatening.
- Hypothyroidism is common and easily managed with hormone replacement. The challenge lies in recognition of signs and symptoms of it for diagnosis.
- Thyroiditis is usually self-limiting.
- Uncontrolled Graves disease and elevated paraneoplastic β-human chorionic gonadotropin levels may predispose individuals to thyroid storm upon experiencing precipitating events.
- The management of severe thyrotoxicosis and thyroid storm involves inhibition of thyroid hormone synthesis, blockade of thyroid hormone release, inhibition of thyroxine-to-triiodothyronine conversion, support for systemic decompensation, and correction of precipitating factors. Rapid inhibition of thyroid hormone synthesis with thionamides followed by blockade of the release of preformed thyroid hormone by iodides is the cornerstone of acute management.
- Octreotide is the primary agent for both prevention and treatment of carcinoid crisis.

Suggested Readings

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Chapter 3
Cardiac Emergencies in Cancer Patients

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Contents

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Chapter Overview

Cardiac problems can occur at any time in cancer patients and be true medical challenges for physicians in an emergency center. The most important symptoms of heart disease include dyspnea, chest pain, chest discomfort, syncope, collapse, palpitation, edema, cough, hemoptysis, and excess fatigue. These symptoms are more common in patients with cancer than in those without it and are frequently nonspecific. Evaluation and management of cardiac emergencies in cancer patients may be challenging and may have to be individualized.

This chapter covers some of the most frequent cardiac emergencies in cancer patients we encounter at our emergency center: cardiac arrhythmias, acute coronary syndrome (ACS), heart failure emergencies, hypertensive emergencies, and pericardial disease-related emergencies. Clinicians must take into account the patient's previous and ongoing cancer treatment to optimize treatment strategies for these emergencies.

Introduction

Cancer patients can present with the usual cardiovascular emergencies as well as other cardiac emergencies that may be related to the cancer itself or side effects of cancer treatment. The assessment and treatment of cardiac emergencies in patients with cancer may differ from those recommended for patients without it depending on the nature and severity of the emergency, the progression of the malignancy, and the patient's general condition. The most common cardiovascular emergencies are summarized in this chapter, with overviews of the diagnostic and therapeutic approaches.

Cardiac Arrhythmias

Cardiac rhythm disturbance is common in cancer patients and can have a variety of symptoms, ranging from none (incidental finding) to life-threatening tachycardia or cardiac arrest. Cancer patients have complex comorbidities that predispose them to

certain arrhythmias and limit their therapeutic options when using antiarrhythmic drugs. Accurate, rapid diagnosis is extremely important to deliver the appropriate therapy.

Etiology

In addition to the typical and traditional causes of cardiac arrhythmia in the general population, cancer patients can have it as a consequence of the malignancy itself or its therapy (Fig. 3.1). Adequate patient management necessitates accurate diagnosis and identification of the mechanisms, potential etiologies, and triggers of these arrhythmias. Table 3.1 lists some of the specific causes of cardiac arrhythmias in cancer patients (Yeh and Bickford 2009; Floyd et al. 2005; Ohnishi et al. 2000).

Diagnosis and Management

When managing cancer patients with suspected acute arrhythmia, emergency care providers should be vigilant and administer treatment to the whole patient and not just for the rhythm disturbance. These patients have complex associated comorbidities, and a rapid heart rate or rhythm irregularities can be simply signs of much more complicated and severe acute illness (e.g., atrial tachycardia or atrial fibrillation in the setting of acute pulmonary embolism, polymorphic ventricular tachycardia triggered by severe metabolic derangements and electrolytes imbalance while taking a QT interval-prolonging agent) (Fig. 3.2).

In the absence of clinical data suggesting otherwise, acute management of cardiac arrhythmia in cancer patients should follow the well-established standard of care guidelines (Blomstrom-Lundqvist et al. 2003), although it can differ slightly from that in patients without malignancies. The difference is mainly related to the choice of antiarrhythmic drugs and atrioventricular (AV)-blocking agents and also the timing and safety of anticoagulation. The selection of these drugs should take into consideration the possibility of drug-drug interactions. For example, diltiazem (Cardizem) and verapamil are potent cytochrome P450 inhibitors that can alter the pharmacokinetics of many chemotherapeutic agents. The QT interval prolongation observed with the use of many cancer therapies can be potentiated by several classes of antiarrhythmic drugs. Also, whether to use short-term or long-term anticoagulation for atrial fibrillation or flutter should be determined carefully in each case, as many patients face increased risk of bleeding in the setting of thrombocytopenia secondary to malignancy or its therapy.

Acute management of arrhythmia in the emergency room starts with the identification of any alarming symptoms resulting from underperfusion of vital organs. These include hypotension, angina, myocardial infarction, heart failure, altered mental status, and shock. For patients presenting with any of these symptoms,

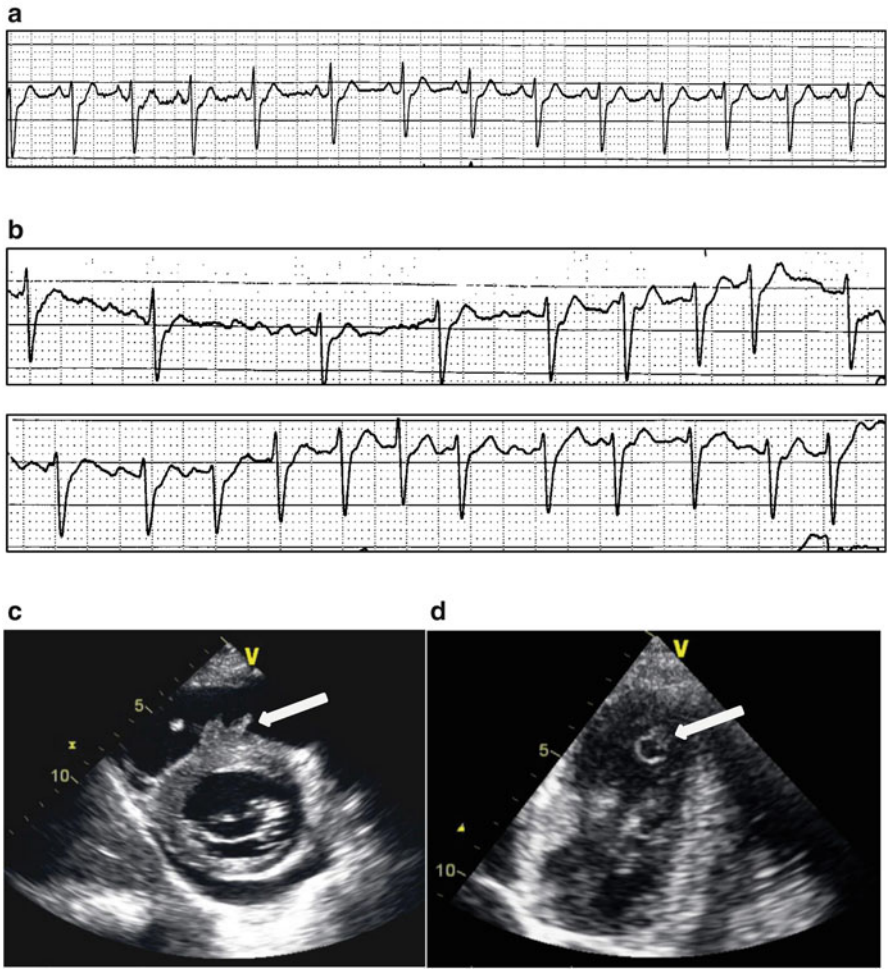

Fig. 3.1 A 36-year-old woman with metastatic thyroid cancer and no prior history of arrhythmia presented to the emergency room with a chief complaint of palpitations. Cardiac monitor tracings demonstrated a baseline sinus rhythm (**a**) with paroxysms of symptomatic supraventricular tachycardia, atrial fibrillation (**b**), and ventricular tachycardia. Echocardiograms demonstrated evidence of multiple metastatic lesions involving the interventricular septum (**c**) and the left ventricular apex (**d**). Myocardial tumor infiltration was felt to be responsible for the arrhythmia

immediate electrical cardioversion is indicated if tachycardia is present, and cardiac pacing is indicated if bradycardia is the cause. For patients with relatively stable hemodynamics, the focus should be establishing a specific diagnosis and mechanism of arrhythmia using 12-lead electrocardiography and the clinical response to vagal maneuvers or drugs. Arrhythmias then can be classified as bradycardia or tachycardia.

Table 3.1 Potential causes of cardiac arrhythmias in patients with malignancy

Malignancy-related
Pericardial infiltration
Myocardial metastasis
Carcinoid valvular heart disease
Carotid compression
Cancer therapy-related
Surgery/radiation therapy involving the neck
Baroreflex failure
Chemotherapy-induced cardiomyopathy
Chemotherapy drug-related
Bradyarrhythmia
Sinus bradycardia (thalidomide, paclitaxel, high-dose steroids, antiemetics)
AV block (paclitaxel)
Tachyarrhythmia
Sinus tachycardia
Atrial fibrillation (vemurafenib)
Atrial tachycardia (ifosfamide)
Ventricular tachycardia (interleukin-2, methotrexate)
QT prolongation/torsades de pointes (arsenic trioxide, vorinostat, nilotinib, lapatinib, dasatinib)

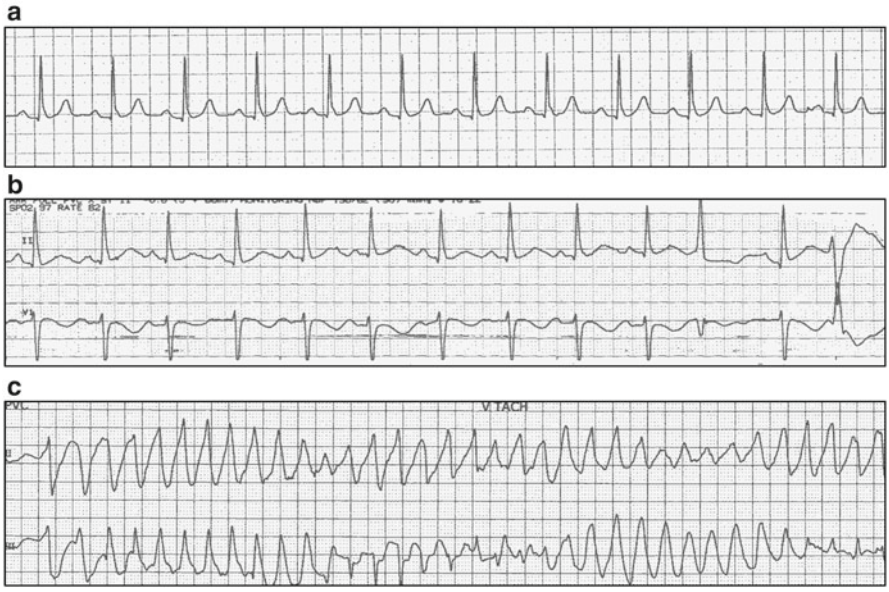

Fig. 3.2 A 68-year-old woman was admitted for recurrent syncope with documented severe hypokalemia (K: 2.8) and hypomagnesemia (Mg: 1.5) while taking voriconazole and ondansetron following chemotherapy (cytarabine and idarubicin) for leukemia. Unlike her previous normal baseline QT interval (**a**), the admission electrocardiogram tracings demonstrated a prolonged QT interval (**b**). She subsequently had documented symptomatic polymorphic tachycardia (**c**) episodes while being monitored

Bradycardia

Bradycardia is defined as a heart rate under 60 beats per minute. A physiologic low heart rate must be distinguished from bradycardia associated with a serious cardiac pathology (e.g., sinus syndrome, heart block).

Etiologies and Mechanisms

A careful review of all medications must be performed to eliminate pharmacotherapy that could lower the heart rate. Certain chemotherapeutic agents have been linked with bradycardia (Table 3.1). The most common of these include paclitaxel and thalidomide. In early phase 1 clinical trials, paclitaxel caused serious hypersensitivity reactions. Thalidomide has been associated with bradycardia at a lower frequency, but the pathophysiology is unclear (Yeh and Bickford 2009).

A less common but equally important cause of bradycardia is baroreflex failure. It is typically characterized by heart rate and blood pressure volatility. Baroreflex failure can arise from abnormalities in the vascular baroreceptors, glossopharyngeal or vagal nerves, or brain stem. This is most often seen in cancer patients who undergo extensive head and neck surgery or receive radiotherapy, which can cause inflammation and scarring of the neck vessels.

Treatment

After identifying and removing any potentially offending agents that can exacerbate bradycardia, treatment must be individualized depending on the symptoms. Careful clinical judgment must be used in determining the cause of the bradycardia and deciding whether it is reversible. For severely symptomatic patients, urgent medical therapy with atropine or an intravenous (IV) inotrope, such as dopamine and epinephrine, may be used. In emergency situations, transcutaneous or transvenous pacemaker therapy may be required to maintain hemodynamic support. Long-term support with permanent pacing will depend on the severity of the symptoms related to the bradycardia and whether it is reversible.

Tachycardia

A clinically useful and practical approach to treating tachycardia permits the classification of it into four categories: irregular, regular narrow QRS complex, wide QRS complex, and polymorphic ventricular tachycardia. A clinically practical stepwise approach to diagnosis and classification of tachycardia is summarized in Fig. 3.3.

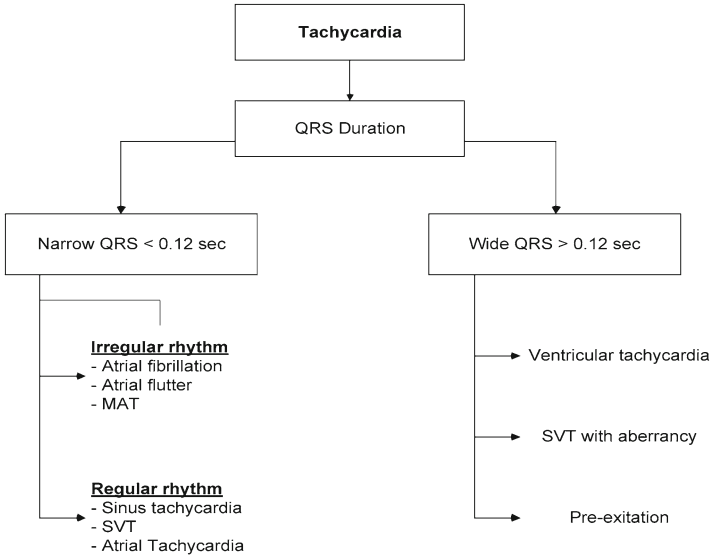

Fig. 3.3 Electrocardiogram-based approach to diagnosis and classification of tachyarrhythmia. *MAT* multifocal atrial tachycardia

Narrow QRS Complex Tachycardia

Narrow QRS complex tachycardia is almost always supraventricular in origin (exceptions are rare) and indicates that electrical conduction occurs through the AV node. Patients with narrow QRS complex tachycardia typically present with palpitations, dizziness, and dyspnea and rarely present with syncope.

Treatment of Regular Narrow QRS Complex Tachycardia

If vagal maneuvers fail in the treatment of narrow QRS complex tachycardia, then treatment with adenosine, β-blockers, or nondihydropyridine calcium-channel antagonists (Cardizem or verapamil) should be tried. Caution is advised when using adenosine in patients with asthma or who have received theophylline (lack of effect) or dipyridamole (potentiates side effects). Atrial fibrillation can occasionally develop following adenosine injections for supraventricular tachycardia (SVT). Immediate termination of the tachycardia suggests SVT (AV nodal re-entrant tachycardia or AV re-entrant tachycardia), whereas lack of response or transient, brief slowing of the heart rate is observed in the settings of sinus tachycardia, atrial tachycardia, atrial fibrillation, and atrial flutter.

Sinus and atria tachycardia are often secondary and triggered by other concomitant acute illnesses or procedures (e.g., infection, pneumonia, pulmonary embolism, surgery). Evaluation and treatment of the primary etiology and its precipitating

causes are effective. In the occasional setting in which atrial tachycardia is persistent or poorly tolerated, pharmacologic intervention with adenosine, β-blockers, nondihydropyridine calcium-channel antagonists, or antiarrhythmic drugs (procainamide, flecainide, propafenone, amiodarone, and sotalol) can be helpful. These drugs have proven to be effective in conversion to sinus rhythm. For rate control, β-blockers, calcium-channel antagonists, and digoxin are effective in blocking the AV node (Blomstrom-Lundqvist et al. 2003).

In the setting of SVT, electrical cardioversion is recommended if tachycardia persists despite the use of vagal maneuvers, carotid massage, adenosine, β-blockers, or calcium-channel antagonists. Use of antiarrhythmic drugs for acute management of SVT is discouraged; they should only be used if the above-mentioned therapeutic measures are ineffective. Flecainide and propafenone are the most preferred antiarrhythmic drugs in the absence of underlying structural heart disease. Procainamide, amiodarone, sotalol, and disopyramide are also effective. In patients with known underlying left ventricular dysfunction, digoxin or amiodarone is preferred.

Treatment of Irregular Narrow QRS Complex Tachycardia

Acute management of atrial fibrillation and atrial flutter in the emergency room follows the general recommendations of urgent cardioversion for hemodynamically unstable patients and initial rate control for stable patients. Ventricular rate control can be achieved using AV-blocking agents like digoxin, β-blockers, and nondihydropyridine calcium-channel antagonists (Cardizem and verapamil). An amiodarone drip can also be considered for rate control in patients with marginal blood pressure or left ventricular dysfunction.

For the subgroup of patients with previously known and documented permanent atrial fibrillation or flutter, controlling the heart rate and reversing the cause of acute decompensation should suffice. For patients with no known prior history of arrhythmia, clinical decision-making regarding acute management is dependent on the arrhythmia. For patients with confirmed arrhythmia durations under 48 h, electrical or chemical cardioversion can be performed safely. Medications with proven efficacy for cardioversion include ibutilide, amiodarone, flecainide, propafenone, procainamide, sotalol, and disopyramide. Those with arrhythmia of unknown duration or suspected duration of more than 48 h have an increased risk of arterial embolization following cardioversion. These patients should receive adequate anticoagulation (e.g., warfarin) or oral direct thrombin inhibitors (e.g., dabigatran) for at least 3 weeks prior to cardioversion and then 4 weeks thereafter. An acceptable alternative is a transesophageal echocardiogram (TEE) in the absence of documented left atrial or left atrial appendage thrombus; cardioversion then can be performed safely, and anticoagulation can be initiated and continued for 4 weeks.

Multifocal atrial tachycardia is typically observed in the setting of lung disease and must be differentiated from atrial fibrillation, as both present as irregular arrhythmias. Antiarrhythmics and cardioversion are ineffective in the setting of multifocal atrial tachycardia. Rate control can be achieved with the use of nondihydropyridine

Table 3.2 Clinical and ECG features favoring ventricular tachycardia

Clinical features	ECG features
Prior myocardial ischemia/ ischemic heart disease	Very wide QRS complex, QRS > 0.16 s
Cardiomyopathy	Positive/negative concordance of precordial leads
Structural heart disease	AV dissociation
Family history of sudden death	Fusion beats
	Capture beats
	Brugada sign (interval from beginning of R wave to deepest part of S > 100 ms)
	Josephson sign (notching near the nadir of the S wave)

calcium-channel antagonists. Anticoagulation is not indicated. Treating the underlying lung process (e.g., chronic obstructive pulmonary disease, hypoxia) can help control this arrhythmia.

Wide QRS Complex Tachycardia

Wide QRS complex tachyarrhythmias (QRS complex greater than 0.12 s) should be classified as one of two distinct entities: ventricular tachycardia or SVT with aberrant conduction. Patients with SVT tend to be hemodynamically stable and present with symptoms similar to those seen in patients with narrow QRS complex tachycardia. Electrocardiographic features may be helpful in distinguishing between SVT with aberrant conduction and ventricular tachycardia (Table 3.2).

Ventricular tachycardia can be a life-threatening rhythm and must be quickly identified and treated. Description of ventricular tachycardia should be based on morphology: monomorphic versus polymorphic. The duration also should be noted: nonsustained versus sustained.

Key electrocardiographic features of ventricular tachycardia include a very wide QRS complex (more than 160 ms), concordance, AV dissociation, fusion beats, and capture beats. Other features, such as Brugada syndrome and Josephson sign, have been helpful in identifying ventricular tachycardia. Ventricular tachycardia can further degrade into ventricular fibrillation, which is represented by chaotic, disorganized electrical activity (Fig. 3.4).

Patients with cancer require special consideration owing to the risk of QT-interval prolongation and torsades de pointes resulting from the use of both chemotherapeutic agents and adjunct medications.

Treatment of Ventricular Tachycardia/Fibrillation

Treatment of hemodynamically significant ventricular tachycardia and ventricular fibrillation should follow Advanced Cardiovascular Life Support standard guidelines established by the American Heart Association (AHA). If the patient is

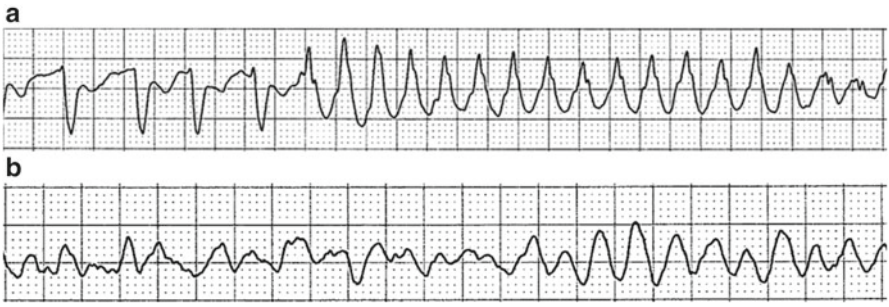

Fig. 3.4 A 68-year-old man with aplastic anemia and severe hypokalemia (K: 2.3) and hypomagnesemia (Mg: 1.5) experienced spontaneous ventricular tachycardia (**a**) that rapidly degraded into ventricular fibrillation (**b**)

hemodynamically compromised, emergent electrical defibrillation should be performed. Antiarrhythmic therapy should be administered under the supervision of a cardiologist when possible. First-line antiarrhythmic therapy includes IV β-blockers, amiodarone (Class III antiarrhythmic), and procainamide (Class Ia antiarrhythmic). IV lidocaine (Class Ib antiarrhythmic) may be reasonable, particularly in the setting of myocardial ischemia or infarction. For torsades de pointes, first-line treatment includes long-acting β-blockers and IV magnesium sulfate (typical dose, 2-g IV push). Secondary medications include isoproterenol in patients with torsades de pointes without prolonged QT intervals. Mexiletine (Class Ib antiarrhythmic) and flecainide (Class Ic antiarrhythmic) may shorten the QT interval and be somewhat effective in patients with prolonged QT intervals (European Heart Rhythm Association et al. 2006).

Ablation therapy may be considered for patients with ventricular tachycardia or fibrillation that is refractory to medical therapy or who are intolerant of it. Use of an implantable cardioverter defibrillator may be indicated in appropriate patients who have survived cardiac arrest or have recurrent syncope despite undergoing medical therapy. Early referral to a cardiac electrophysiologist is recommended for further evaluation and treatment of recurrent or symptomatic ventricular arrhythmias.

Treatment of SVT with Aberrancy

Therapy for SVT with aberrancy should follow the recommendations for narrow QRS complex tachycardia described above.

ACS

ACS is a major cause of morbidity and mortality in the developed world and accounts for approximately 2.5 million hospitalizations worldwide and more than 1.4 million hospitalizations in the United States annually. Investigators have

performed significant research in this field. However, little remains known about ACS in cancer patients. Working in a large cancer center enables our involvement in caring for a large number of cancer patients with ACS, but the uniqueness of the patient population and diversity of cancer treatment limit the capacity to generalize and provide solid guidelines regarding this subgroup of patients with ACS.

Definition

ACS includes a continuum of clinical presentations covered by the following range of diagnoses: unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). UA and NSTEMI are also called non-ST-elevation ACS to distinguish them from STEMI.

The symptoms of UA result from myocardial ischemia caused by an underlying imbalance between supply and demand of myocardial oxygen. UA is defined as angina pectoris that can present with one of three features: (1) occurs at rest or with minimal exertion and usually lasts more than 20 min (if not interrupted by treatment with nitroglycerin); (2) new-onset, severe, frank pain; and (3) a crescendo pattern (more severe, prolonged, or increased pain). Some patients with prolonged pain at rest have evidence of myocardial necrosis according to their levels of cardiac serum markers (creatine kinase muscle-brain fraction, troponin T or I, or both) and have an NSTEMI.

Pathogenesis

The most common cause of UA and NSTEMI is plaque rupture and coronary thrombosis with compromise of blood flow to a region of viable myocardium. Fissure or rupture of these plaques and consequent exposure of core constituents (lipid, smooth muscle, and foam cells) to the bloodstream leads to the local generation of thrombin and deposition of fibrin. This in turn promotes platelet aggregation and adhesion and intracoronary thrombus formation. UA and NSTEMI are generally associated with white, platelet-rich, and only partially occlusive thrombi. In many cases, this myonecrosis is thought to result from downstream microembolization of platelet aggregates from a ruptured unstable plaque. In contrast, patients with an STEMI (or Q-wave myocardial infarction) have red, fibrin-rich, and more stable occlusive thrombi. Acute coronary occlusions leading to STEMI tend to cluster in predictable "hot spots" within the proximal third of the coronary arteries. Other less common causes of UA and NSTEMI are dynamic obstructions (e.g., coronary spasm in patients with Prinzmetal angina), progressive mechanical obstructions, inflammation, infections, and secondary UA as a result of mismatch between supply and demand (e.g., anemia).

Diagnosis

The initial diagnosis of ACS is based on history, risk factors, and echocardiography findings. The patient's history is of the utmost importance in the recognition of acute myocardial infarction. The typical presentation may not be typical in critically ill cancer patients, and physicians should have high indices of suspicion with any patient who presents with new congestive heart failure (CHF), ventricular arrhythmia, hypotension, heart murmur of mitral insufficiency, or systemic embolic events or who were resuscitated from apparent sudden death. Serial serum measurements of cardiac enzymes and serial ECGs should be performed for such patients.

As many as half of all cases of ACS are clinically silent and, consequently, go unrecognized by the patient. In addition, elderly patients may only present with altered mental status.

Risk factors for ACS include male sex, diabetes mellitus, smoking history, hypertension, advanced age, hypercholesterolemia, and prior cerebrovascular accident or peripheral vascular disease in general.

UA and NSTEMI are closely related conditions with similar clinical presentations. Distinction between them depends on whether the ischemia is severe enough to cause myocardial necrosis that can lead to the release of detectable quantities of intramyocardial biomarkers. Cardiac troponin I and T are the preferred biomarkers, as they are more specific and reliable than creatine kinase or its isoenzyme creatine kinase muscle-brain fraction.

ECGs are similar in patients with UA and NSTEMI and can have transient or persistent ST-segment depressions and T-wave flattening or inversion in the ECG leads reflecting the location of the myocardium in jeopardy. Also, patients with metastatic cancer involving the heart may have ECG abnormalities that resemble those seen in patients with myocardial ischemia.

Physical examination may exclude important differential diagnoses, such as chest wall lesions, irradiation burns, masses, pleuritis, pericarditis, and pneumothorax. It also may reveal evidence of ventricular failure and hemodynamic instability.

Early Risk Stratification

The Thrombosis in Myocardial Infarction (TIMI) risk score is a commonly used risk-stratification tool. The predictable variables in this score are (1) age greater than 65 years, (2) more than three conventional risk factors for coronary artery disease, (3) known coronary artery stenosis greater than 50 %, (4) ST-segment deviations on presenting ECGs, (5) more than two anginal events within the prior 24 h, (6) use of aspirin within 7 days, and (7) elevated serum cardiac marker levels.

Management

Tailoring treatment of ACS to risk in cancer patients not only ensures that patients who will benefit the most receive aggressive treatment but also prevents potentially hazardous treatment in those with poor prognoses. The treatment approach should take into account the status of the patient's cancer to avoid unnecessary procedures or actions that can delay cancer treatment. At the other end of the spectrum, suboptimal treatment of ACS may significantly decrease the patient's ability to complete cancer treatment and survive the disease. Initial medical treatment of ACS includes bed rest and use of oxygen and opiate analgesics to relieve pain, anti-ischemic medications, and antiplatelet/antithrombotic drugs.

Anti-Ischemic Therapy

Class I recommendations for anti-ischemic therapy include bed rest, use of supplemental oxygen as needed, and sublingual/IV administration of nitroglycerin for ongoing symptoms in the absence of contraindications.

β-blockers are central to treatment of ACS, which is reflected in the 2012 and 2013 American College of Cardiology (ACC) Foundation/AHA guidelines (2012 Writing Committee Members et al. 2012; O'Gara et al. 2013). Oral β-blockade for UA and NSTEMI is a Class Ia recommendation in the absence of heart failure, a low output state, increased risk of cardiogenic shock, age greater than 70 years, systolic blood pressure less than 120 mm Hg, sinus tachycardia greater than 110 bpm, heart rate less than 60 bpm, or any other relative contraindication. IV β-blockade is now reserved for specific indications, such as ongoing rest pain, especially with tachycardia or hypertension. Patients at lower risk are those who tend to gain the most from β-blockade. IV β-blockade is specifically avoided in patients with heart failure, hypotension, or hemodynamic instability.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are recommended as Class I therapy for UA and NSTEMI in patients with pulmonary congestion or a left ventricular ejection fraction less than 0.40 in the absence of hypotension. ACE inhibitors improve short- and long-term survival after myocardial infarction complicated by left ventricular dysfunction (Studies of Left Ventricular Dysfunction, Survival and Ventricular Enlargement, and Trandolapril Cardiac Evaluation trials) and should be administered (preferably orally) within 24 h and continued upon discharge unless contraindicated. In patients with intolerance to ACE inhibitors, angiotensin-receptor blockers can be considered as alternative therapy.

Other Class I recommendations include (1) use of nondihydropyridine calcium-channel blockers (verapamil or Cardizem) in cases of β-blocker intolerance with an absence of contraindications and (2) discontinuation of nonsteroidal anti-inflammatory drugs (both nonselective and cyclooxygenase-2–specific agents) owing to increased risk of ischemic events and myocardial rupture.

Antiplatelet/Antithrombotic Therapy

Platelet aggregation and thrombus formation play key roles in the development of ACS. Recent advances in treatment, such as low-molecular-weight heparin, glycoprotein (GP) IIb/IIIa inhibitors, and clopidogrel, and the increasingly safe and widespread use of percutaneous coronary intervention (PCI) have raised questions about optimal antiplatelet/antithrombotic management.

Antiplatelet Therapy

Antiplatelet therapy for ACS is achieved by balancing the extent of platelet activation using a combination of antiplatelet drugs having complementary actions: aspirin, thienopyridines, and GP IIb/IIIa inhibitors.

Aspirin

Use of aspirin is the cornerstone of antiplatelet therapy and irreversibly acetylates platelet cyclooxygenase-1, thereby blocking the production of prostaglandin G2 and thromboxane A2. In patients with ACS, aspirin should be administered as soon as possible and continued indefinitely unless the patient is intolerant of it (Class I). Patients with platelet counts as low as 17 k/mL have taken aspirin as antiplatelet therapy, but no therapeutic recommendations can be made until more data on aspirin are available (Yusuf et al. 2010).

Adenosine Diphosphate Receptor Antagonists

Ticlopidine and clopidogrel inhibit platelet activation by irreversibly blocking surface adenosine diphosphate receptors. Thienopyridines are recommended as Class I therapy for UA and NSTEMI in an initial noninvasive strategy or as an alternative to GP inhibitors in an early invasive pathway. Ticlopidine is infrequently used owing to the rare but potentially life-threatening side effects of severe neutropenia and thrombotic thrombocytopenic purpura. Clopidogrel administration at a loading dose of 300–600 mg followed by a maintenance dose of 75 mg daily is a Class I recommendation as both a conservative approach and as an alternative to GP IIb/IIIa receptor inhibitors in an early invasive strategy. In addition, clopidogrel should be administered to UA and NSTEMI patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance.

Considering that data suggest that administration of 600 mg of clopidogrel prior to and after PCI is beneficial, the debate now extends to the optimal timing of clopidogrel use in patients with UA or NSTEMI. Early treatment with clopidogrel reduces the incidence of early ischemic events, benefitting those who ultimately receive PCI, but increases the risk of bleeding if the patient's coronary anatomy is unknown.

Coronary artery bypass grafting (CABG) is a possibility in these patients. About 50–60 % of patients presenting with ACS will receive PCI, and 8–20 % are considered for CABG. Early identification of patients who may need urgent CABG using TIMI risk score tools may help in identifying those who should not receive early 600-mg loading doses of clopidogrel, minimizing the bleeding risk in those proceeding to CABG, and preserving benefit for the majority of patients needing PCI. Although the optimal timing, dosing, and duration of treatment with clopidogrel remain undetermined, our approach in cancer patients includes an early TIMI score, and if bypass is not considered, we load patients with 600 mg of clopidogrel.

Proton pump inhibitors are often administered to patients in combination with thienopyridines to help reduce the risk of bleeding after ACS or PCI. Their use is even greater in cancer patients. Several studies have demonstrated that proton pump inhibitors, especially omeprazole, can diminish the antiplatelet effects of clopidogrel. However, at present, scarce data demonstrate a definitive interaction between proton pump inhibitor use and the clinical benefit of clopidogrel (Gilard et al. 2008).

Ticagrelor is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor P2Y12 that has a more rapid onset and more pronounced platelet inhibition than clopidogrel. In patients having ACS with or without ST-segment elevation, treatment with ticagrelor produced a lower rate of death from vascular causes, myocardial infarction, or stroke than did treatment with clopidogrel without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding.

The optimal ticagrelor dosing strategy as determined according to the agent's pharmacokinetic and pharmacodynamic profile is a loading dose of 180 mg followed by 90 mg orally twice a day. Within 30 min, a ticagrelor loading dose of 180 mg has resulted in roughly the same level of platelet aggregation inhibition as that achieved 8 h after administration of a clopidogrel loading dose of 600 mg.

Ticagrelor blocks reuptake of adenosine by red blood cells, which leads to cardiovascular benefit via reduced blood pressure, improved coronary flow, or protection against reperfusion injury. This explains why some patients experience bradycardia and dyspnea with the use of ticagrelor. Use of ticagrelor is a promising approach to the prevention of cardiovascular events in patients with ACS.

Anticoagulation

The heparins include unfractionated heparin (UFH), low-molecular-weight heparin, and fondaparinux, a synthetic heparin pentasaccharide that primarily acts by neutralizing factor Xa.

UFH, the prototype of all heparin derivatives, is a standard antithrombotic therapeutic for ACS in all patients regardless of the treatment approach. Parenteral anticoagulation with IV UFH or subcutaneous low-molecular-weight heparin should be added to antiplatelet therapy with aspirin or a thienopyridine (Class I recommendation). UFH is usually administered by IV injection followed by infusion, starting

with weight-adjusted doses. The activated partial thromboplastin time is used to monitor anticoagulation in most circumstances, although the activated clotting time is used when higher intensity anticoagulation is required (e.g., during PCI, with cardiopulmonary bypass).

Plaque disruption with resultant platelet activation and leukocyte-platelet aggregation is the pathophysiologic process common to both ACS and PCIs. Treatment with low-molecular-weight heparins has caused less platelet activation than that with unfractionated heparin.

Enoxaparin has demonstrated advantages over UFH in low- to moderate-risk patients with non-ST-elevation ACS treated using a conservative strategy. Enoxaparin is a safe and effective alternative to UFH with the advantages of convenience and a trend toward producing a lower rate of nonfatal myocardial infarction with a modestly excessive risk of bleeding. Enoxaparin is preferable to UFH as an anticoagulant in patients with UA or NSTEMI in the absence of renal failure and/or need for CABG (Class IIa recommendation). PCI can be performed safely in patients with UA or NSTEMI who have received the typical dose of enoxaparin.

Physicians have used dalteparin in an early invasive strategy in moderate- to high-risk patients with non-ST-elevation ACS, resulting in sustained benefit at 5 years of follow-up. Dalteparin appears to be safe in combination with abciximab in patients with UA undergoing coronary intervention. Abciximab-based therapy during coronary interventions rapidly reduces the amount of platelet degranulation and number of leukocyte-platelet aggregates.

Fondaparinux is a synthetic heparin pentasaccharide that acts via antithrombin to exclusively neutralize factor Xa. Regimens using enoxaparin, UFH, or fondaparinux have established efficacy in patients in whom a conservative strategy is selected. In patients in whom a conservative strategy is selected and who have an increased risk of bleeding, fondaparinux is preferable. Administration of fondaparinux is not recommended prior to or during primary PCI in patients with STEMI owing to an increased risk of guiding-catheter thrombosis. Patients with UA, NSTEMI, or STEMI undergoing any PCI should not receive fondaparinux as the sole anticoagulant. Use of an anticoagulant with antithrombin activity (e.g., UFH) is recommended as adjunct therapy with PCI even if the patient received prior treatment with fondaparinux.

GP IIb/IIIa Inhibitors

The typical pharmacotherapeutic strategy for patients with non-ST-elevation ACS has been an intensive combination of aspirin, clopidogrel, and GP IIb/IIIa inhibitors (abciximab, tirofiban, and eptifibatide) along with an antithrombin (UFH or low-molecular-weight heparin). Recent clinical trials challenged the role of GP IIb/IIIa-based strategies and suggested new treatment options that differ by omitting GP IIb/IIIa-based antiplatelet therapeutics. A consequence of the resulting data has been a variety of pharmacotherapeutic regimens that differ from the ACC/AHA guidelines. For example, the threshold for administering GP IIb/IIIa inhibitors is even higher in

patients receiving ongoing treatment of cancer (chemotherapy, radiation therapy, or surgery), which is driven mainly by increased risk of bleeding.

Because the pharmacotherapeutic approaches for non-ST-elevation ACS requiring PCI are complicated by a myriad of evolving antiplatelet strategies that have existed experimentally and outside our current evidence-driven guidelines, the optimal use of GP IIb/IIIa receptor antagonists involves identifying the appropriate patients, window for therapy, drug, and dosing. Heterogeneity in clinical trials has borne a mixture of data suggesting both benefit and equivalence, making interpretation difficult for both clinical and interventional cardiologists. High-risk patients with non-ST-elevation ACS requiring PCI are most likely to benefit from treatment with GP IIb/IIIa receptor antagonists when they have ongoing ischemia, dynamic ECG changes, and troponin positivity owing to unstable plaque with active inflammation.

When platelets are activated, the surface GP IIb and IIIa undergo a change in conformation that increases their affinity for binding to fibrinogen and other ligands, resulting in platelet aggregation. The platelet GP IIb/IIIa receptor antagonists act by occupying the receptors and preventing fibrinogen from binding, thereby preventing platelet aggregation. Experimental and clinical studies have suggested that occupancy of at least 80 % of the receptor population and inhibition of platelet aggregation to adenosine diphosphate by at least 80 % result in potent antithrombotic effects. The various GP IIb/IIIa antagonists have significantly different pharmacokinetic and pharmacodynamic properties. Available data suggest that the combination of eptifibatide and clopidogrel provides greater antiplatelet activity than does clopidogrel alone. How this translates to improved clinical outcomes remains to be evaluated.

The Intracoronary Stenting and Antithrombotic Regimen trials examined the necessity of treating coronary artery disease with GP IIb/IIIa inhibitors in various patient populations and settings and with various pharmacotherapeutic regimens. GP IIb/IIIa receptor blockade limits the ischemic complications of PCI across all indications, among various devices, and with multiple anticoagulation approaches using a variety of agents. Future guidelines should provide more specific direction regarding risk stratification in an era in which GP IIb/IIIa receptor blockade and clopidogrel may be used in concert in patients with non-ST-elevation ACS who undergo PCI.

Heparin-Induced Thrombocytopenia Patients

In 10 % of patients receiving treatment with UFH for 5 days or more, heparin-induced thrombocytopenia is known to develop and is usually reversible after heparin withdrawal. Alternative agents used effectively in patients with heparin-induced thrombocytopenia include lepirudin, argatroban, bivalirudin, and danaparoid, although the last agent is not available in North America. Fondaparinux is used in a small number of patients with heparin-induced thrombocytopenia and generally appears to be safe. (Please refer to the Hematologic Emergencies chapter for more discussion on heparin-induced thrombocytopenia.)

Anti-inflammatory Treatment

Treatment with HMG-CoA reductase inhibitors and diet adjustment for low-density lipoprotein cholesterol levels greater than 100 mg/dL begin 24–96 h after hospital admission and continue at discharge. In addition, treatment with fibrates or niacin is recommended if the high-density lipoprotein cholesterol level is less than 40 mg/dL, whether as an isolated finding or in combination with other lipid abnormalities.

Cancer Treatment and ACS

Antimetabolites such as 5-fluorouracil (FU) are known to cause an ischemic syndrome that resolves upon cessation of treatment and administration of anti-ischemic medications. 5-FU can cause symptoms in patients without pre-existing coronary artery disease, but the incidence is higher in patients with underlying coronary artery disease (1.1 % and 4.5 %, respectively). Patients should be observed closely, and)5-FU administration should be discontinued if cardiac symptoms develop. Previously, the pathogenesis of ischemia was presumed to be related to coronary vasospasm. However, failure to illicit significant vasospasm with infusions of ergonovine and 5-FU during cardiac catheterization has diminished the veracity of this hypothesis (Frickhofen et al. 2002). Alternative theories suggest the causative mechanisms to be direct cardiotoxicity, interaction of 5-FU with the coagulation system, and autoimmune responses through the accumulation of citrate in myocardial cells via interference of fluoroacetate with the Krebs cycle (Frickhofen et al. 2002). In 1 study of 427 patients, those receiving continuous infusions of 5-FU and leucovorin for more than 5 days had markedly higher rates of cardiotoxicity than did those receiving continuous infusions without leucovorin or those receiving short courses of infusions (Tsavaris et al. 2002). These results confirmed that the cardiotoxic effect of 5-FU is largely schedule-dependent. Rechallenge with 5-FU should be reserved only for patients with no reasonable alternative therapy and should be performed in the setting of aggressive prophylaxis and close monitoring.

Adverse cardiac effects seem to appear far less frequently than in the past, although some tyrosine kinase inhibitors have induced cardiotoxicity to a certain degree. Thus, the use of sunitinib has resulted in a decline in ejection fraction by 10 %, and the use of sorafenib has led to cardiac ischemia in 3 % of patients.

The relatively increased rate of cardiac events in our patients also may be related to a high frequency of hypertension. Furthermore, development of microembolism as an additional cause of cardiac damage cannot be entirely excluded, so concomitant antithrombotic treatment may be reasonable. This is supported by findings of myocardial necrosis with normal coronary arteries, conduction disturbances (which may arise from embolism of the AV nodal artery), and the occurrence of noncardiac vascular events in two patients.

Bevacizumab is the first vascular endothelial growth factor inhibitor approved by the U.S. Food and Drug Administration for systemic use in cancer patients. The

incidence of myocardial ischemia was approximately 0.6–1.5 % in a pooled analysis of 1745 patients receiving bevacizumab in five randomized controlled trials (Yeh and Bickford 2009). In these trials, age greater than 65 years and a history of arterial thrombotic events were risk factors for ischemia. Vascular endothelial growth factor promotes proliferation and survival of vascular endothelium, and inhibition of the reparative pathway in endothelial cells may lead to endothelial cell dysfunction. As a result, vascular trauma related to underlying atherosclerosis may lead to exposure of subendothelial collagen, which will then promote the coagulation cascade that ultimately leads to arterial thrombosis and acute coronary ischemia (Kamba and McDonald 2007; Kilickap et al. 2003). Unfortunately, the risk of ischemia is not related to the duration of therapy. Therefore, patients who receive bevacizumab must be appropriately screened for cardiovascular risk factors and should undergo evaluation for underlying coronary disease prior to starting therapy when indicated.

Conservative Versus Early Invasive Strategy

Conservative treatment involves intensive medical management followed by risk stratification via noninvasive means (usually stress testing) to identify patients who may need coronary angiography. Patients with a TIMI risk score of at least 3 have benefited significantly from an early invasive strategy, whereas those with a score of no more than 2 have not. In addition, in cancer patients in our practice, exposure to cardiotoxic medications and history of irradiation of the chest are added to the TIMI score. Therefore, a patient positive for cardiac markers and with a history of cardiotoxic chemotherapy and irradiation of the chest has an initial "cancer TIMI score" of at least 3 in our practice and should be considered for early angiography (ideally within 24 h), with the goal of revascularization via PCI or bypass surgery.

Conclusions

Cancer patients presenting to an emergency center with symptoms compatible with ACS should undergo full treatment according to the ACC/AHA guidelines unless they have contraindications. A multidisciplinary team approach (emergency care, cardiology, oncology, and critical care) is required, as tailoring the treatment to the patient's comorbidities is of paramount importance.

Heart Failure Emergencies in Cancer Patients

Acute heart failure is a common occurrence in the U.S. population and has increasingly become a reason for presentation to the emergency room and hospital admission at The University of Texas MD Anderson Cancer Center. In this section, we

Table 3.3 Chemotherapy agents associated with left ventricular dysfunction

Anthracyclines
Doxorubicin
Epirubicin
Idarubicin
Monoclonal antibody-based tyrosine kinase inhibitors
Trastuzumab
Bevacizumab
Small-molecule tyrosine kinase inhibitors
Dasatinib
Imatinib
Sunitinib
Alkylating agents
Cyclophosphamide
Ifosfamide
Antimetabolites
Clofarabine

highlight some acute presentations of heart failure that require urgent attention, diagnostic tools that may aid the physician in making a clinical diagnosis of heart failure, and treatment options. Furthermore, we present some special considerations for acute heart failure conditions that we have experienced at our institution. For example, cancer patients are at risk for heart failure owing to the use of various therapies that may contribute to left ventricular dysfunction. Cardiotoxicity of chemotherapeutic agents, which depends on the cumulative dose, concomitant use of other cardiotoxic agents, and administration schedule, is an important focus of our cardiology practice. The most common agents linked with the development of cardiotoxic effects are anthracyclines, alkylating agents, and monoclonal antibody-based tyrosine kinase inhibitors. Table 3.3 lists the common chemotherapeutic agents associated with left ventricular dysfunction (Yeh and Bickford 2009). We also highlight some treatment strategies that preliminarily have been beneficial in patients with left ventricular dysfunction associated with chemotherapy.

Definition and Classification

Acute heart failure is the rapid onset of signs and symptoms of abnormal systolic or diastolic heart function. Patients present with a myriad of symptoms that the European Society of Cardiology classified into the six clinical groups listed below.

1. Acute decompensated heart failure: de novo, or as decompensation of CHF.
2. Hypertensive acute heart failure: signs and symptoms of heart failure are accompanied by high blood pressure and relatively preserved left ventricular function, with a chest radiograph compatible with acute pulmonary edema.

3. Pulmonary edema (verified by a chest X-ray) accompanied by severe respiratory distress, with crackles over the lung and orthopnea, featuring O_2 saturation, usually less than 90 % on room air prior to treatment.
4. Cardiogenic shock: evidence of tissue hypoperfusion induced by heart failure after correction of preload. Cardiogenic shock is usually characterized by reduced blood pressure (systolic blood pressure less than 90 mm Hg or a drop in the mean arterial pressure of more than 30 mm Hg) and/or low urine output (less than 0.5 mL/kg/h), with a pulse rate greater than 60 bpm with or without evidence of organ congestion. A continuum from low cardiac output syndrome to cardiogenic shock exists.
5. High output failure: characterized by high cardiac output, usually with a high heart rate (caused by arrhythmia, thyrotoxicosis, anemia, Paget disease, or iatrogenic or other mechanisms), with warm peripheries, pulmonary congestion, and sometimes low blood pressure as in cases of septic shock.
6. Right heart failure: characterized by low output syndrome with increased jugular venous pressure, increased liver size, and hypotension.

Diagnosis

Heart failure should be diagnosed clinically, relying heavily on the patient's clinical history and physical examination. However, the etiology of CHF (Table 3.4) may be difficult to discern; laboratory, radiologic, and echocardiographic studies can aid in confirming the clinical diagnosis. The presentation of patients with heart failure can vary from very mild symptoms, such as dyspnea, to cardiogenic shock, in which the degree of cardiac dysfunction does not meet the demands of the body. Often, patients present with hypotension, pulmonary edema, and poor perfusion of their organ systems and extremities.

The Framingham criteria are the most accepted criteria for diagnosis of heart failure. To establish a diagnosis of heart failure, either two major or one major and two minor criteria must be present. The Framingham major criteria are jugular vein distension, rales, paroxysmal nocturnal dyspnea or orthopnea, cardiomegaly, acute pulmonary edema, S3 gallop, hepatojugular reflex, and venous pressure greater than 16 cm of water. The minor criteria are ankle edema, dyspnea on exertion, pleural effusion, tachycardia (greater than 120 bpm), hepatomegaly, night cough, and vital

Table 3.4 Possible etiologies of congestive heart failure

Coronary disease	Valvular disease	Infiltrative disease	Other
Acute myocardial infarction Myocardial ischemia Mechanical complications of myocardial infarction	Aortic stenosis Aortic regurgitation Mitral stenosis Mitral regurgitation	Amyloidosis Glycogen storage disease	Takotsubo cardiomyopathy Peripartum Hypertension Myocarditis Toxic or metabolic chemotherapy

Table 3.5 Initial tests recommended for evaluation of patients presenting with heart failure (ACC/AHA)

Complete blood count; urinalysis; measurement of serum electrolyte (including calcium and magnesium), blood urea nitrogen, serum creatinine, and fasting blood glucose (glycohemoglobin) levels; lipid profile; liver function tests; and measurement of thyroid-stimulating hormone level
Twelve-lead electrocardiogram and chest radiograph
Two-dimensional echocardiography with Doppler should be performed to assess left ventricular ejection fraction, left ventricular size, wall thickness, and valve function

capacity reduction of one third from maximum. A criterion that can be either major or minor is weight loss of 4.5 kg or more in 5 days in response to treatment.

The ACC/AHA further classifies heart failure into four groups (Hunt et al. 2009): Class I, asymptomatic; Class II, mild symptoms with moderate exertion; Class III, symptoms with minimal activity; and Class IV, symptoms at rest.

The ability of a clinician to rapidly assess the patient, develop a differential diagnosis, and introduce appropriate indicated therapy is of the utmost importance. The ACC/AHA recommends a panel of routine blood tests and radiologic and cardiac studies for all patients with heart failure (Table 3.5) (Hunt et al. 2009).

Another examination advocated to help decipher the etiology of heart failure symptoms is the brain natriuretic peptide (BNP) test. Patients with CHF often have other comorbidities, and determining whether symptoms are predominantly related to heart failure or noncardiac causes such as chronic obstructive pulmonary disease exacerbation, pulmonary embolism, and large symptomatic pleural effusion becomes difficult. The use of a BNP or N-terminal pro-BNP test can help differentiate cardiac causes of dyspnea from other causes. Researchers have suggested that a BNP level greater than 500 pg/mL likely results from CHF, whereas a level less than 100 pg/mL is unlikely to be caused by CHF. Values ranging from 100 to 500 pg/mL require further investigation (European Heart Rhythm Association et al. 2006).

Treatment

Treatment of acute heart failure in patients presenting with signs and symptoms of it is aimed at providing symptomatic relief via volume management and oxygen saturation maintenance. Treating the underlying cause of the initial decompensation is equally important. Therapy often involves use of oxygen, morphine, diuretics, vasodilators, or inotropes, and in refractory and severe cases, it includes mechanical support with intra-aortic balloon pumps or a left ventricular assist device.

Five factors should be considered in the treatment of CHF:

1. Maintenance of arterial oxygen saturation within the normal range (95–98 %) to maximize tissue oxygenation, helping prevent end-organ dysfunction. This sometimes requires the use of noninvasive positive pressure ventilation, which reduces breathing effort and metabolic demand.

2. Vasodilator therapy is indicated in patients with adequate blood pressure to lower preload and afterload. This is especially important in patients with hypertensive acute CHF. Nitrates can be administered to lower blood pressure.
3. Diuretic therapy is indicated in patients with CHF and symptoms secondary to fluid retention. Diuretic dosing should be individualized based on the patient's clinical condition and titrated to clinical response.
4. Inotrope administration is indicated in patients who exhibit peripheral hypoperfusion but are not candidates for or whose heart failure is refractory to diuretic and vasodilator therapy. The use of inotropes is potentially harmful owing to the incidence of arrhythmia, and patients should be closely observed in an intensive care unit with invasive hemodynamic monitoring. Typical inotropes used in patients with CHF are dobutamine at 2–20 μg/kg/min and milrinone at 0.375 μg/kg/min. Dobutamine acts on the B1 and B2 receptors to produce dose-dependent positive inotropic and chronotropic effects and a reflex decrease in peripheral vascular resistance. This can lead to increased renal blood flow in response to increased cardiac output and improved diuresis. Milrinone is a phosphodiesterase inhibitor that has significant inotropic, lusitropic, and vasodilating effects, such as increased cardiac output, decreased pulmonary wedge pressure, and systemic vascular resistance.
5. Mechanical assist devices can be used temporarily in patients whose heart failure is not responding to conventional therapy. Intra-aortic balloon pumps may be indicated in patients with cardiogenic shock or severe acute heart failure that does not respond to conventional medical treatment. Intra-aortic balloon pumps are contraindicated in the setting of significant aortic insufficiency or aortic dissection. Ventricular assist devices are mechanical circulatory support pumps that can partially unload the ventricle, decrease myocardial demand, and increase end-organ flow.

Special Considerations in Cancer Patients

Diagnosis and treatment should be rapidly initiated as described above for any patient presenting with signs and symptoms of acute CHF. However, from our experience at MD Anderson, a few common clinical presentations are worthy of note. One that we have seen increasingly is stress cardiomyopathy, or Takotsubo cardiomyopathy. Also referred to as broken heart syndrome, it is frequently precipitated by a stressful event and has a clinical presentation that is often indistinguishable from a myocardial infarction. The syndrome classically occurs in postmenopausal women, the typical presenting symptoms are dyspnea and chest pain, and it is associated with emotional or physical stress in the majority of patients. ST elevation is the most common electrocardiographic abnormality in patients with Takotsubo cardiomyopathy; however, this finding varies markedly. Often, patients also have modest elevation in the levels of cardiac biomarkers. Echocardiography shows transient akinesis or hypokinesis of the left ventricular mid-segment with or without apical segment involvement and

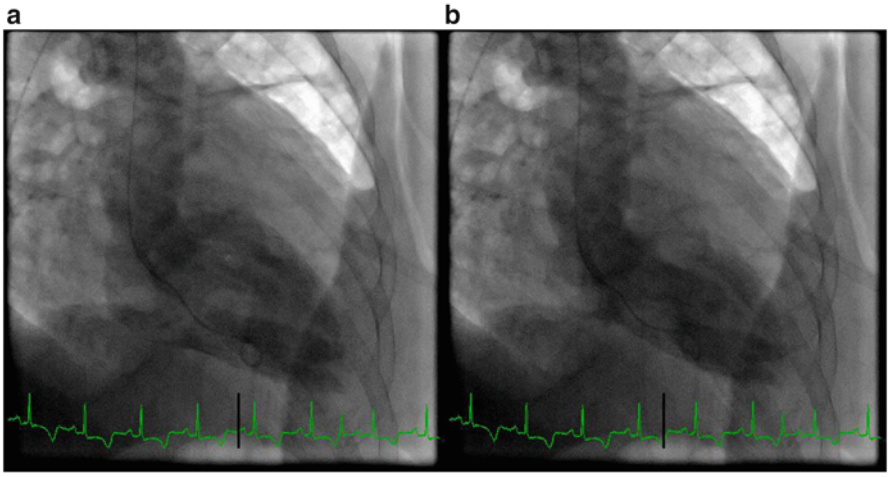

Fig. 3.5 Takotsubo cardiomyopathy. (**a**) Diastolic and (**b**) systolic frames from a left ventriculogram demonstrating contractile basal segments and an akinetic apex

preservation of basal systolic function (Fig. 3.5). Wall-motion abnormalities extend beyond a single epicardial vascular distribution. Importantly, obstructive coronary disease and acute plaque rupture are absent from coronary angiograms. The prognosis in these patients is usually excellent, with complete resolution of the systolic dysfunction and wall-motion abnormalities within days to weeks.

Furthermore, a substantial number of chemotherapeutic drugs are associated with the development of cardiotoxic effects. Treatment in cancer patients should be similar to that in any patient who presents with acute CHF, with special consideration directed at the prevention of cardiotoxic effects. The rate of anthracycline cardiotoxicity is reported to be as high as 26 % at a cumulative dose of 550 mg/m^2 but much lower (3–5 %) at a cumulative dose of 400 mg/m^2 (Wouters et al. 2005), highlighting the importance of administering a safe cumulative dose to the patient. Other strategies include altering the infusion speed, using alternative chemotherapeutic drugs, changing the administration schedule, and using cardioprotectants such as dexrazoxane. Also, authors have reported data supporting the use of β-blockers and ACE inhibitors in patients with anthracycline-induced cardiomyopathy (Cardinale et al. 2006). Furthermore, researchers have shown that carvedilol prophylactically protects both systolic and diastolic function in patients receiving anthracycline-based chemotherapy (Kalay et al. 2006).

Hypertensive Emergencies in Cancer Patients

Hypertensionis reported to be the most common comorbidity in patients with malignancies (37 %) (Piccirillo et al. 2004). Its prevalence in cancer patients before chemotherapy is similar to that in the general population (29 %) (Maitland et al. 2010).

A much higher rate is observed after the initiation of certain chemotherapeutic agents (angiogenesis inhibitors, 17–80 %; alkylating agents, 36–39 %; immunosuppressants after stem cell transplantation, 30–80 %). The most frequently used chemotherapeutic agents known to cause hypertension include several of the angiogenesis inhibitors commonly known as vascular signaling pathway inhibitors. Hypertension is emerging as one of the most common side effects of these agents. The incidence of de novo or worsening hypertension in association with these drugs varies from 17 to 80 %. These drugs include the anti-vascular endothelial growth factor antibody bevacizumab and certain tyrosine kinase inhibitors (sunitinib, sorafenib, and pazopanib). The hypertension mechanism is not well understood and continues to be investigated (Fig. 3.6). Investigators have proposed several theories, including endothelial dysfunction associated with reduced nitric oxide bioavailability and increased vascular and renal endothelin production, increased vascular tone, vascular rarefaction (decreased microvessel density), and renal thrombotic microangiopathy with secondary glomerular structural and functional changes that lead to proteinuria and hypertension. In the absence of a proven dominant mechanism, the real cause is likely to be a combination of several of the suggested mechanisms (Table 3.6).

Other classes of chemotherapeutic agents are known to induce hypertension via several mechanisms: alkylating agents and calcineurin can cause endothelial dysfunction and arterial vasoconstriction, calcineurin can activate the renin-angiotensin system, and steroids can increase patients' sensitivity to vasoactive substances and contribute to salt and fluid retention.

Other cancer therapy modalities known to be associated with hypertension include radiation therapy and surgery involving the head and neck area, leading to baroreflex failure immediately after surgery or years after radiation therapy. The mechanisms of hypertension in this setting include severe, variable alteration in the autonomic pathways connecting the baroreceptors and carotid bodies to the brain stem. This causes an imbalance in the sympathetic and parasympathetic systems, leading to severe hypertensive crisis and four well-described syndromes (Ketch et al. 2002).

1. Hypertensive crisis: typically occurs following neck surgery and is associated with loss of the vagus and glossopharyngeal nerves. Severely elevated systolic blood pressure can range from 200 to 300 mm Hg.
2. Volatile hypertension: the most common form, it develops insidiously. It is caused by a predominant loss of parasympathetic tone, resulting in excessive sympathetic discharge. Symptoms are similar to those encountered with pheochromocytoma (labile blood pressure, headache, dizziness, tachycardia, and anxiety).
3. Orthostatic tachycardia: this is also related to parasympathetic tone loss to the sinus node, leading to positional sinus tachycardia. This syndrome can subsequently evolve to a volatile form of hypertension.
4. Malignant vagotonia: this is the least common form and is caused by increased parasympathetic tone, leading to severe bradycardia with associated hypotension or hypertension.

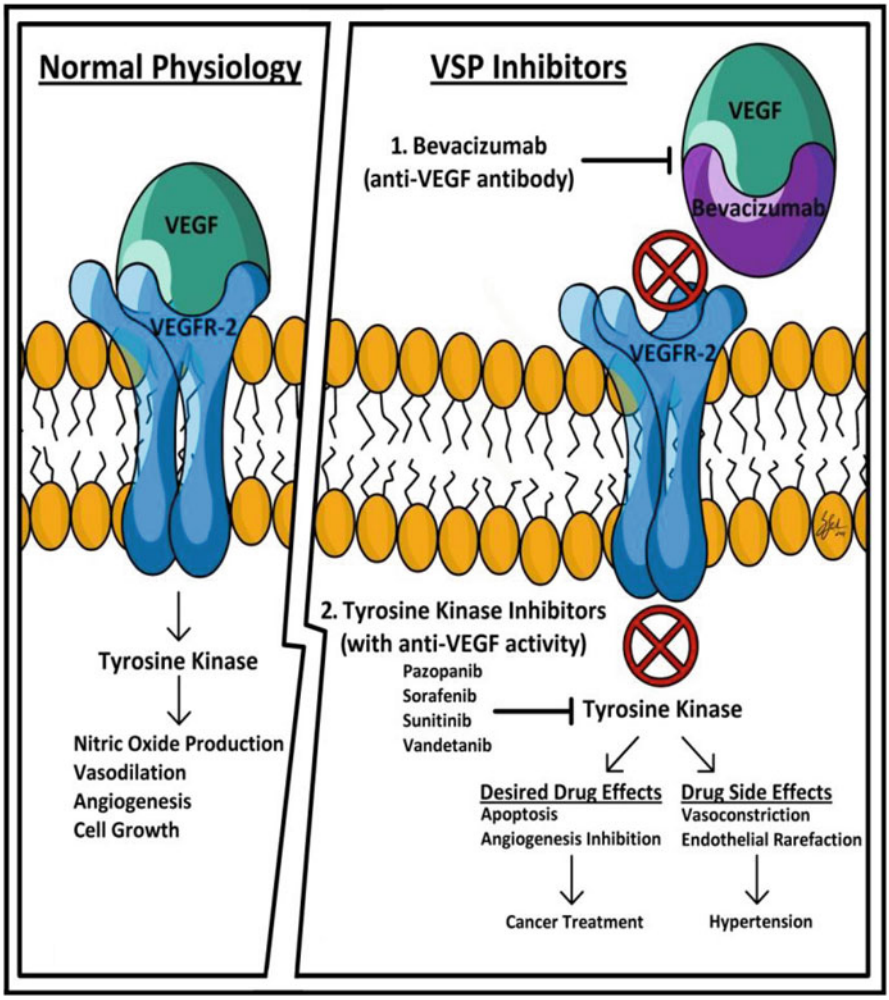

Fig. 3.6 *Left*: vascular endothelial growth factor (VEGF) is secreted and binds to the VEGF receptor. This binding triggers intracellular signaling pathways, including tyrosine kinase, leading to nitric oxide production, vasodilation, angiogenesis, and cell growth. *Right*: VEGF signaling pathway (VSP) inhibitors work through various mechanisms. Bevacizumab binds to VEGF and prevents activation of the VEGF receptor, whereas tyrosine kinase inhibitors prevent the activation of tyrosine kinase. The desired effect of these medications is promotion of apoptosis and angiogenesis inhibition, leading to cancer treatment. The undesired effect of hypertension is a result of vasoconstriction and decreased nitric oxide production. [Adapted from Mouhayar E. Cardiovascular Complications of Cancer Therapeutic Agents. In: Bonow RO, Mann DL, Zipes DP, Libby P (eds). *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia, PA: Saunders; 2011. With permission from Elsevier.]

Management of baroreflex failure includes use of clonidine, guanethidine, and sometimes diazepam for management of hypertension and a cardiac pacemaker for malignant vagotonia and bradycardia.

Table 3.6 Summary of overall incidence, suspected mechanisms, and time to hypertensive effect associated with certain chemotherapeutic agents

Medications	Overall incidence of hypertension (%)	Time to hypertensive effect	Mechanism of hypertension
Angiogenesis inhibitors			
Anti-VEGF antibody			1. Reduce nitric oxide bioavailability 2. Increase endothelin 3. Increase vascular tone 4. Vascular rarefaction 5. Renal thrombotic microangiopathy
Bevacizumab	4–35	First dose and any time after	
Tyrosine kinase inhibitors			
Pazopanib	40–47	Within 10 days in 39 % of patients	
Sorafenib	17–43	After 3 weeks of therapy	
Sunitinib	15–34	First 3–4 weeks of therapy	
Vandetanib	33	First 3 months of therapy	
Alkylating agents			
Busulfan	36	Associated with intravenous injections	1. Endothelial dysfunction 2. Arterial vasoconstriction
Cisplatin	39	Within few months to years after therapy	
Calcineurin inhibitors			
Cyclosporine	60–80	As early as first dose; often becomes chronic	1. Arterial vasoconstriction 2. Activation of the renin-angiotensin system
Tacrolimus	30	Within weeks of initiation	
Immunosuppressants			
Mycophenolate moefetil	28–78	Within 1–6 months of therapy	Exact mechanism is not well understood
Mammalian target of rapamycin inhibitors			
Sirolimus	45–49	Any time in therapy; risk is elevated when combined with cyclosporin	
Other			
Steroids	20	Dose-related; can be seen with first dose	1. Fluid and salt retention 2. Increase sensitivity to vasoactive substances
Erythropoietin	13.7–27.7	As early as 2 weeks or as late as 4–5 months	1. Increase endothelin 2. Reduce nitric oxide 3. Activation of the renin-angiotensin system

VEGF vascular endothelial growth factor

Another mechanism of cancer therapy-induced hypertension is renal artery stenosis caused by accelerated atherosclerosis following irradiation of the abdomen. Therapies include antihypertensive medications and, occasionally, revascularization (angioplasty or surgery).

Historically, the reported prevalence and management of cancer therapy-related hypertension has differed markedly among specialists. This is partly related to the fact that internists and cardiologists typically follow the Joint National Committee classification and guidelines for the evaluation and treatment of high blood pressure, whereas oncologists are more familiar with the Common Terminology Criteria for Adverse Events. These criteria are intended for reporting trial-based side effects and are not meant to guide hypertension management. As awareness of the importance of early recognition and management of hypertension has increased, in 2009, the National Cancer Institute updated the Common Terminology Criteria for Adverse Events (version 4) to be in agreement with Joint National Committee staging. With these changes, increased incidence of hypertension is likely be reported in future oncologic clinical trials.

Elevated blood pressure is common in cancer patients seen in the emergency room. A large number of these patients have elevated blood pressure secondary to pain and other physical or emotional stresses associated with their cancer diagnosis and treatment. Blood pressure in this setting will rapidly decline after simply treating the source of pain or relieving the patient's anxiety. Aggressive use of antihypertensive medications in this setting should be avoided. For patients who present with the primary finding of new-onset or worsening hypertension and without clinical data suggesting otherwise, the management of cancer treatment-related hypertension should follow the Joint National Committee 7 classification and guidelines. Management should focus on minimizing the risk of end-organ damage, decreasing associated morbidities, and allowing for continuation of required cancer therapy. Choosing an antihypertensionmedication should take into consideration three main factors: (1) the mechanism and pathophysiology of the blood pressure elevation (e.g., use of calcium-channel blockers for vasoconstriction-mediated hypertension caused by calcineurins, use of diuretics for steroid-induced hypertension), (2) the possibility of drug-drug interactions that can lead to potentiated toxicity of both chemotherapeutic and antihypertension medications, and (3) a compelling indication for use or avoidance of a specific antihypertensive agent (e.g., use of β-blockers in patients with prior myocardial infarction or ACE inhibitors in patients with CHF) (Mouhayar and Salahudeen 2011). Another important consideration is agents that may have compelling indications in patients with specific types of cancer or with certain cancer therapies. For example, the use of β-blockers in patients with malignant melanoma has been associated with an overall reduced risk of cancer progression by 36 % (De Giorgi et al. 2011). Larger epidemiologic studies and randomized clinical trials are required to substantiate these findings, although consideration of these agents as first-line therapy for melanoma may be useful.

Another important point is the potential risks and benefits of using medications that target nitrous oxide or angiotensin II production when selecting management strategies for patients receiving specific agents like the vascular signaling pathway

inhibitors. Because these anticancer agents cause vasoconstriction in part via decreased nitrous oxide production, medications such as nitrates, phosphodiesterase-5 inhibitors, and nebivolol, a nitric oxide-producing β-blocker, seem to be beneficial in theory. However, a concern is that by targeting this pathway, these medications may compromise the efficacy of the antitumor treatment. Given this theoretical risk, using caution with these agents until more safety and efficacy trials are conducted may be prudent. On the other hand, angiotensin II is a potent proangiogenic growth factor, and experimental trials have demonstrated that blocking its synthesis with the use of ACE inhibitors or angiotensin receptor blockers can produce antiangiogenic effects. Because of this potential benefit, these agents should be considered for patients without hyperkalemia, renal failure, or other contraindications. More evidence is needed to determine the true role of these agents in vascular signaling pathway inhibitor-related hypertension.

Occasionally, patients present with hypertensive crisis, defined as a systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 120 mm Hg. Hypertensive crisis is considered a hypertensive emergency when it is associated with end-organ damage (encephalopathy, papilledema, worsening angina, myocardial infarction, CHF, or acute renal failure). Immediate treatment and rapid lowering of blood pressure are indicated. Asymptomatic patients with no evidence of end-organ damage are classified as having hypertensive urgency. The treatment goal in these patients is a gradual decrease in blood pressure to a target of 160/100 mm Hg over several hours to days, as researchers have not demonstrated a clear benefit of more rapid reduction.

Target blood pressure control and medication choice depend on the severity of the clinical presentation of hypertension. Hypertensive urgency can often be managed using oral agents. For patients already receiving treatment of hypertension, emphasizing the importance of dietary and medication compliance in addition to increasing the dose of currently used antihypertensive drugs or adding another agent often suffices. For those with confirmed untreated hypertension, a low dose of a short-acting diuretic (20 mg of IV furosemide), ACE inhibitor (6.25–12.5 mg of captopril), or clonidine (0.1–0.2 mg) can be used followed by initiation of a long-acting agent. The patient then can be discharged home safely after a few hours of observation and assertion of adequate response to initial medications. Close clinical follow-up over a few days is important to confirm the patient's clinical response and adherence to therapy. Hypertensive emergency is treated more aggressively and requires hospitalization. The choice of therapeutic agents and target blood pressure differ based on the presenting syndrome. Patients with hypertensive encephalopathy need a modest acute drop in blood pressure (25–30 %) within the first 24 h. Nitroprusside and labetalol are the drugs of choice in such cases. Patients with associated aortic dissection, on the other hand, should first receive β-blockers (labetalol), aiming for a heart rate below 60 bpm and systolic blood pressure below 120 mm Hg. In the setting of associated ACS, β-blockers and IV nitroglycerin effectively lower blood pressure. Drugs that can increase cardiac workload and O_2 demand, such as hydralazine, are contraindicated. Although oral ACE inhibitors are good options, use of IV ACE inhibitors in the setting of concomitant myocardial infarction is discour-

aged based on proven poor outcomes. Patients with CHF and pulmonary edema benefit from taking diuretics and IV vasodilators such as nitroprusside and nitroglycerin. Table 3.7 lists the most commonly used IV drugs in the setting of hypertensive crisis, including their doses, mechanisms of action, and most common side effects.

In summary, new or worsening hypertension is commonly encountered in cancer patients. Causes include many of the therapeutic agents used to treat cancer. These patients occasionally seek initial care for hypertension and hypertensive crisis in the emergency room. Diagnosis and treatment should follow the Joint National Committee 8 guidelines (James et al. 2014) with the aim of minimizing the risk of end-organ damage and enabling continuation of required cancer therapy. A team approach involving collaborative efforts between oncologists and other specialists (emergency room physicians, internists, cardiologists, and nephrologists) is encouraged for optimal management of hypertension. Future studies must determine how the management of hypertension can influence—positively or negatively—cancer therapy and outcomes.

Pericardial Disease-Related Emergencies in Cancer Patients

In patients with cancer, the pericardium is the most common site of malignant involvement of the heart via both direct tumor extension and hematogenous spread. Patients with malignancy-related pericardial disease present to the emergency room with a variety of complaints related to pericardial syndromes resulting from the malignancy itself or its therapy (Table 3.1). These syndromes include acute pericarditis, pericardial effusion with or without tamponade, and right-sided heart failure related to constrictive pericarditis. Prompt diagnosis and management of these conditions are particularly important to prevent a potentially catastrophic outcome.

The nature and severity of the presenting symptoms, the complexity of associated comorbidities, and the cancer-related prognosis have a major impact on the choice of treatment modality for pericardial disease-related emergencies. The spectrum of therapeutic options is wide, ranging from simple medical therapy with analgesics and anti-inflammatory medications to complex percutaneous and surgical interventions to palliative care. Management in these patients requires close cooperative efforts and direct communication among primary oncologists, emergency room physicians, cardiologists, cardiothoracic surgeons, and palliative care specialists.

Acute Pericarditis

Acute pericarditis is an acute inflammatory process involving the pericardial sac. Chest pain related to acute pericarditis is a common clinical presentation in the emergency room. Etiologies include direct tumor invasion, irradiation of the chest, medications, chest surgery, and infection (Table 3.8). The pain is typically pleuritic in nature, radiating to the neck and shoulders. It is partially relieved by sitting up but

Table 3.7 Intravenous medications for hypertensive crises

Drug	Dose	Indications/mechanism of action	Adverse effects
Sodium nitroprusside	0.25–10 mcg/kg/min	Any patient; venous and arterial vasodilator	Cyanide toxicity, nausea, vomiting
Labetalol	20–80 mg IV bolus followed by drip at 0.5–2.0 mg/min or 20–80 mg IV every 15 min	Any patient except those with decompensated heart failure	Orthostatic hypotension, heart failure exacerbation, bradycardia
Nicardipine	5–15 mg/h	Any patient, caution in patients with angina; calcium channel blocker vasodilator	Reflex tachycardia, nausea, vomiting
Nitroglycerin	5–200 mcg/min	Acute myocardial infarction, angina, or heart failure symptoms; vasodilator	Headache, nausea, tachyphylaxis
Hydralazine	5–10 mg IV every 4–6 h (not to exceed 20 mg/dose)	Any patient, avoid in patients with acute myocardial infarction; vasodilator	Reflex tachycardia, headache, angina exacerbation
Enalaprilat	0.625–1.250 mg IV every 6 h	Avoid in patients with acute myocardial infarction, renal failure, or hyperkalemia; ACE inhibitor	Renal insufficiency, hyperkalemia
Fenoldopam	0.1–1.6 mcg/kg/min	Any patient; calcium channel blocker vasodilator	Hypotension, headache, angina exacerbation
Esmolol	500-mcg/kg bolus over 1 min followed by 50–300 mcg/kg/min by infusion	Avoid in patients with underlying bradycardia or decompensated congestive heart failure; β-blocker	First-degree heart block, congestive heart failure, asthma
Phentolamine	5–10 mg as IV bolus, 1–2 min/10–30 min	Pheochromocytoma; hypertensive crisis	Tachycardia, orthostatic hypotension, angina exacerbation

worsens in the supine position. Fever and pericardial friction rub can be present, but patients with them often have unremarkable physical examinations. The initial evaluation of a patient with acute pericarditis should include an ECG, a chest X-ray, measurement of cardiac biomarkers (creatine kinase, creatine kinase muscle-brain fraction, or troponin), and 2-dimensional echocardiography. Diagnosis is based on history and physical examination and supported by the presence of diffuse ST elevation on ECGs (Fig. 3.7). The white blood count and sedimentation rate are typically elevated in patients with pericarditis, but these values have very limited specificity in patients with malignancies, as baseline values are altered secondarily to cancer, chemotherapy, and concomitant infections. Serial cardiac biomarker levels are typically normal in these patients. An elevated troponin or creatine kinase muscle-brain fraction level reflects myocardial necrosis and should raise concern about possible acute myocardial infarction or myopericarditis. Echocardiography is helpful in the assessment of segmental wall-motion abnormalities and associated pericardial effusion. A normal study does not rule out pericarditis.

Table 3.8 Potential causes of pericardial disease (pericarditis/pericardial effusion) in cancer patients

Malignancy
Lung cancer
Breast cancer
Lymphoma
Leukemia
Esophageal cancer
Infection
Viral, bacterial, tuberculosis, fungal
Cancer therapy
Chest irradiation
Chemotherapy
5-FU
Anthracyclines (doxorubicin, daunorubicin)
Cytarabine
Cyclophosphamide
Bleomycin
Dasatinib (effusion)
Chest and mediastinal surgery

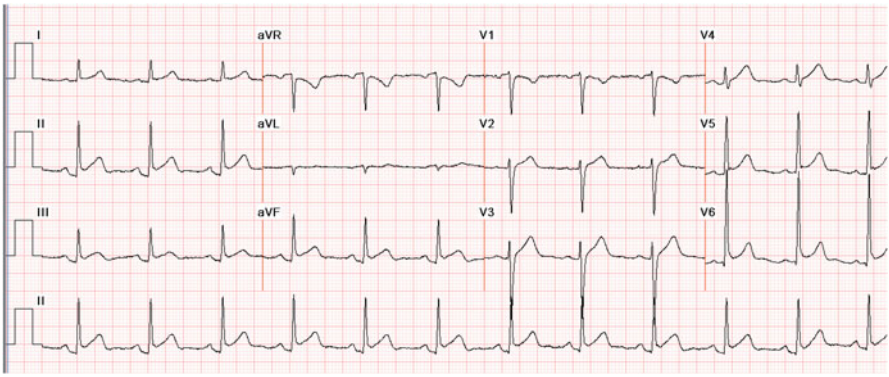

Fig. 3.7 Electrocardiogram demonstrating diffuse ST elevation with PR depression in a 47-year-old woman presenting with severe, pleuritic chest pain for days with normal cardiac biomarker levels. The electrocardiographic findings are consistent with acute pericarditis

A lack of randomized trials makes management of acute pericarditis in cancer patients mainly an empiric approach that is often extrapolated from management recommendations for idiopathic pericarditis. Hospitalization is indicated if the initial presentation is associated with high-risk clinical features, including moderate to large effusion, tamponade physiology, concomitant myopericarditis, high fever, and poorly controlled chest pain (Imazio 2011). Otherwise, patients can undergo treatment on an outpatient basis. Medical management includes bed rest, analgesia, and anti-inflammatory agents. Acute pericarditis typically responds well to treatment with standard agents, including aspirin (650 mg every 4–6 h) and nonsteroidal anti-inflammatory drugs like ibuprofen (400–800 mg every 6–8 h) and indomethacin

(75–150 mg daily) for 2–4 weeks (Imazio 2011). In cases of concomitant thrombocytopenia, nonsteroidal anti-inflammatory drugs and aspirin are relatively contraindicated. Treatment failure is often related to short treatment courses or the use of inappropriately low doses. The addition of colchicine to aspirin (0.5 mg twice daily for 3 months, once daily if weight is less than 70 kg) has proven to be beneficial in reducing pain acutely as well as reducing recurrent pericarditis (Imazio et al. 2010b). Colchicine is typically used as an adjunct treatment rather than monotherapy. The most common reported side effect of colchicine is diarrhea. In patients with hematologic disorders and recent stem cell transplant recipients, the clinical benefit of colchicine use should be carefully balanced against the rare but serious potential side effect of myelosuppression (Lotrionte et al. 2010). Although corticosteroid use is reported to be highly effective in treating chemotherapy-related pericarditis, routine use is typically discouraged owing to the serious side effects of corticosteroids, including treatment failure and recurrent pericarditis. However, steroids can be used in patients with thrombocytopenia or pericarditis secondary to certain chemotherapeutic drugs (Table 3.8). Whereas certain guidelines emphasize the importance of using high-dose steroids for recurrent pericarditis (1.0–1.5 mg/kg prednisone) for at least 1 month with a tapering regimen over 3 months, a recent meta-analysis demonstrated that use of low-dose steroids (0.2–0.5 mg/kg prednisone daily) is associated with reduced treatment failure rates and recurrence (Lotrionte et al. 2010). Anticoagulation is strongly discouraged and should be used with caution to minimize the chance of causing effusion and secondary tamponade.

Pericardial Effusion and Tamponade

The pericardial sac contains a small amount of pericardial fluid (25–35 mL) under normal physiologic conditions. This sac has very limited ability to distend with large amounts of pericardial effusion, especially when fluid accumulates rapidly. Not all effusions necessitate treatment or urgent intervention. Pericardial effusion becomes an emergency when symptoms develop or when pericardial or echocardiographic findings demonstrate impending or frank tamponade physiology in asymptomatic patients. Tamponade occurs when the rate of fluid accumulation overwhelms and surpasses the sac compliance properties. The pericardial space pressure then exceeds the cardiac chamber pressure, causing the chambers to become increasingly susceptible to collapse. This can be caused by rapid, sudden fluid accumulation or following a drop in cardiac filling pressure caused by dehydration or diuresis in a patient with previously stable and compensated effusion. Potential causes of pericardial effusion and tamponade in cancer patients are listed in Table 3.8.

Symptomatic patients with pericardial effusion or tamponade usually present with fatigue, dyspnea, syncope, or arrhythmia. Physical examination findings include sinus tachycardia, distended jugular veins, pulsus paradoxus (greater than 10-mm Hg drop in systolic blood pressure during inspiration), lower extremity edema, hypotension, and even shock. Usual ECG findings include low QRS voltage, electrical alternans, and nonspecific ST- and T-wave changes. Chest X-rays can

show cardiomegaly ("water bottle" silhouette). Echocardiography is the diagnostic test of choice because it can help establish the diagnosis and guide management. Pericardial effusion size is typically graded as minimal, small, moderate (less than 2 cm), or large (more than 2 cm). Fibrous strands are frequently seen in the pericardial space on ECGs but are difficult to differentiate from occasional tumor masses invading the pericardial space. Echocardiographic evidence of tamponade includes chamber collapse and inferior vena cava plethora. In addition, demonstration of exaggerated respiratory variation in mitral and tricuspid valve inflow is useful in assessing the hemodynamic significance of an effusion and in diagnosing tamponade. Cardiac catheterization is rarely needed or used but can be helpful if echocardiographic findings are inconclusive.

Medical management of pericardial effusion and tamponade is limited to pain control if pericarditis is present. IV fluid infusion is helpful only when the patient has evidence of hypovolemia. Excessive volume infusion in the absence of hypovolemia does not improve hemodynamics and can be theoretically detrimental, as expanding right ventricular volume can lead to a secondary drop in left ventricular filling by potentiating ventricular interdependence. Otherwise, stable, asymptomatic effusions can be managed safely with observation and careful monitoring, as no other medical therapies or interventions have any proven roles. Definitive treatment of pericardial tamponade often necessitates fluid drainage. This can be accomplished using echocardiography, fluoroscopy, or computed tomography-guided pericardiocentesis (Fig. 3.8). A sample of the pericardial fluid should be sent for laboratory testing and

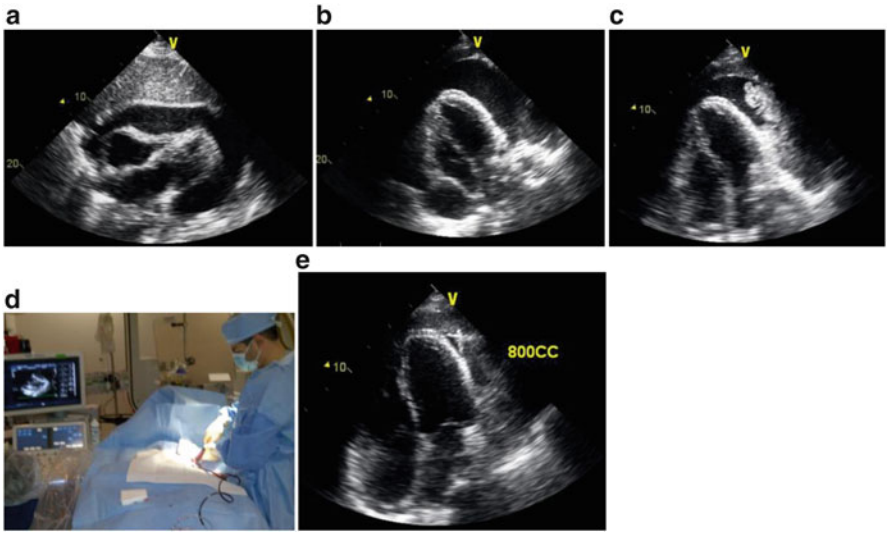

Fig. 3.8 Echocardiogram study demonstrated a large pericardial effusion with associated tamponade physiology in a 73-year-old woman with breast cancer and new-onset dyspnea. (**a**) Large effusion in the subcostal view with evidence of right ventricular collapse. (**b** – **e**) Apical 4-chamber views demonstrating effusion before (**b**) and during (**c** and **d**) pericardiocentesis. The bright density in the pericardial space (**d**) represents saline contrast bubble injection used to confirm the position of the catheter tip in the pericardial space. (**e**) Echocardiogram demonstrating minimal residual effusion after evacuation of 800 mL of fluid

to help establish the etiology. A draining catheter is typically kept in place for 3–5 days or until a volume of less than 25 mL is drained in 24 h. This approach has been associated with lower recurrence rates than has simple drainage. Patients' symptoms and hemodynamics improve rapidly after effusion drainage.

Physicians have used local infusion of chemotherapeutic (thiotepa, carboplatin, cisplatin, and mitoxantrone) and sclerosing (tetracycline and bleomycin) agents for initial and recurrent effusions. The benefits of these agents regarding patient mortality and prevention of effusion recurrence are not well defined. Authors have reported cases of worsening pericardial disease and progression to constrictive pericarditis following the use of sclerosing drugs (Imazio et al. 2010a).

Creation of a pleuropericardial window is another approach to managing tamponade and recurrent effusion. However, use of this procedure is associated with significant morbidity. It is performed via surgical incision in the subxiphoid area. Other modalities reported to have good success rates include thoracoscopy and percutaneous balloon catheter-guided pericardial windows. Extreme caution is required when putting patients under general anesthesia for such procedures, as mechanical ventilation and the vasodilatory effect of anesthesia can reduce afterload and worsen cardiovascular hemodynamic instability with secondary refractory hypotension and shock.

Constrictive Pericarditis

A rare syndrome, constrictive pericarditis is usually related to chronic inflammation of the pericardium, causing pericardial thickening with secondary impaired filling of cardiac chambers and diastolic dysfunction. In cancer patients, constrictive pericarditis can develop secondarily to tumor infiltration of the pericardial sac following irradiation of the chest area, after transient pericarditis, or secondarily to sclerotherapy for pericardial effusion. Clinically, patients present with signs and symptoms of right-sided heart failure, including peripheral edema, ascites, weight gain, and liver dysfunction. ECG findings include atrial arrhythmia, low QRS voltage, and nonspecific ST- and T-wave changes. Pericardial sac thickening (greater than 3 mm) can be seen on ECGs, magnetic resonance images, and computed tomography scans of the chest. Hemodynamic data obtained via Doppler echocardiography and cardiac catheterization are required to confirm the diagnosis and can help differentiate constrictive pericarditis from restrictive cardiomyopathy. Diuretics can be used for initial relief of symptoms and management of volume overload, but definitive treatment of constrictive pericarditis necessitates pericardiectomy.

Key Practice Points

- Arrhythmia in cancer patients can be a sign of a much more complicated and severe acute illness. Management of it can differ slightly from that in patients without malignancies when it comes to use of antiarrhythmic drugs and timing and safety of anticoagulation. Many cardiac medications are cytochrome P450 inhibitors and can alter the pharmacokinetics of many chemotherapeutic agents. QT prolongation observed with many cancer therapies can be potentiated by several classes of antiarrhythmic drugs.
- The treatment approach for ACS should take into account the status of the patient's cancer to avoid unnecessary procedures or actions that can delay cancer treatment.
- Aspirin is the cornerstone of antiplatelet therapy for ACS. Nevertheless, its use in patients with thrombocytopenia should be based on specific clinical circumstances rather than the absolute platelet count.
- A BNP level greater than 500 pg/mL likely results from CHF, whereas levels less than 100 pg/mL are unlikely to be caused by CHF.
- Takotsubo cardiomyopathy is seen frequently in patients at MD Anderson.
- Targeting a cumulative anthracycline dose less than 400 mg/m^2 decreases the rate of anthracycline-induced cardiotoxicity.
- De novo or worsening hypertension is common in cancer patients. Etiologies include many of the therapeutic modalities used in these patients. The treatment aim is to minimize the risk of end-organ damage and enable continuation of required cancer therapy.
- Definitive treatment of pericardial tamponade often necessitates fluid drainage using echocardiography, fluoroscopy, or computed tomography-guided pericardiocentesis. A draining catheter is typically kept in place for 3–5 days, aiming for catheter-mediated pericardiodesis. This approach has been associated with recurrence rates lower than those associated with simple drainage.

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Chapter 4
Pulmonary and Airway Emergencies

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Chapter Overview

Shortness of breath (dyspnea) is a very debilitating and cancer therapy-limiting symptom. It can occur during cancer treatment, in the supportive phases, or at the end of life. It is a cause of worry, anxiety, and physical distress to the patient when he or she is unable to take breaths or when taking ineffective breaths. Breathing may be painful and is described by patients as shortness of breath. Some causes of dyspnea are easy to manage with clever arrival at an easily treatable diagnosis, whereas prolonged hospitalization is required to manage other causes.

Introduction

Dyspnea in the cancer patient may be related to the cancer or a pre-existing disease, or it may be multifactorial. The subjective sensation of shortness of breath is similar to that in any patient without cancer. Shortness of breath may not correlate with objective clinical findings, but proceeding with a systematic approach to management of dyspnea in patients who have it is important (Fig. 4.1). The goal of

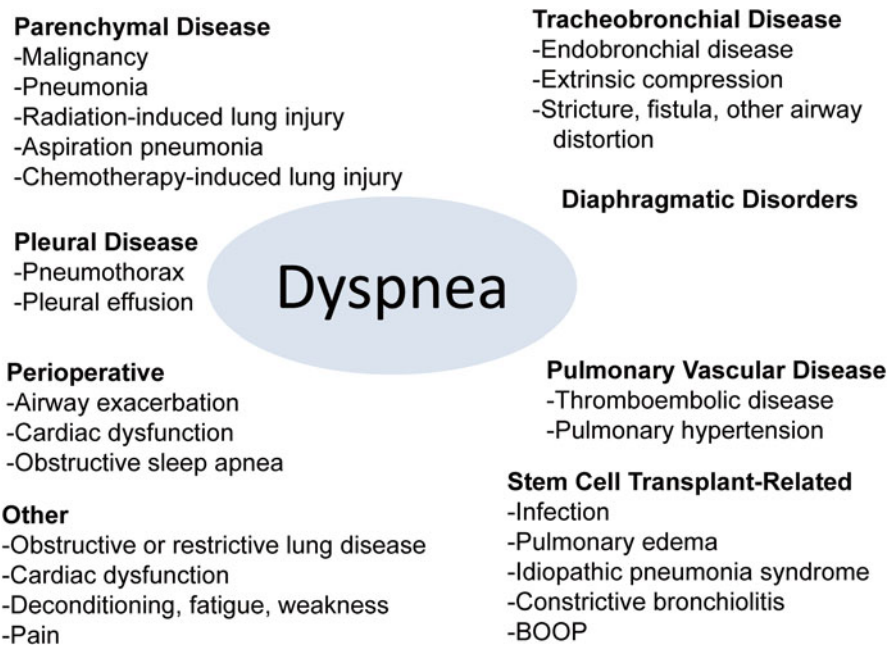

Fig. 4.1 Etiologies of dyspnea in cancer patients. *BOOP* bronchiolitis obliterans organizing pneumonia

this chapter is not to address in detail all of the potential causes of dyspnea but rather to selectively describe the etiologies of conditions commonly seen in cancer patients. Pulmonary infections and acute venous thromboembolic disease are discussed in detail in other chapters.

Pneumothorax

Pneumothorax may be classified as spontaneous, iatrogenic, or tension pneumothorax or hydropneumothorax. Etiologies for pneumothorax include procedural complications (pleural or central venous access), pleural metastatic disease, infections (necrotizing pneumonia, *Pneumocystis jirovecii*), therapy sequelae (radiation, radiofrequency ablation), and underlying chronic lung disease. Authors have reported spontaneous pneumothorax associated with successful chemotherapy for lung metastasis.

Clinical manifestations of pneumothorax include acute dyspnea, hypoxemia, and subcutaneous emphysema. Pneumomediastinum and pneumoperitoneum can be attributed to spontaneous pneumothorax, as well.

Treatment of pneumothorax is based on radiologic criteria and clinical symptoms. The diagnosis may be confirmed using chest radiography, computed tomography (CT), or ultrasonography. Interventions include supplemental oxygen, aspiration of air, and placement of a chest tube or surgery. Small pneumothoraces (less than 10–15 % of hemithorax) in stable patients can be observed clinically and with serial chest radiographs. In comparison, symptomatic patients with larger pneumothoraces (greater than 15 % of hemithorax) should undergo interventions. If a pneumothorax does not improve, including radiologically, after intervention, the physician should evaluate the patient for other causes of dyspnea.

Pleural Effusion

Malignant pleural effusion can occur with all types of cancer and usually suggests advanced disease (Shannon et al. 2010b). Malignancies that commonly cause malignant pleural effusions include lung, breast, ovarian, gastrointestinal cancers and lymphoma. Cancer can metastasize hematogenously or contiguously. Other etiologies for malignant pleural effusion include tumor emboli to visceral pleura and tumor seeding from visceral to parietal pleura (Uzbeck et al. 2010). Pleural metastases do not necessarily result in pleural effusion in all cases, and not all pleural effusions in cancer patients are caused by malignancy. Confirmation of malignancy via pleural fluid cytology or pleural biopsy is recommended.

Clinical manifestations of malignant pleural effusion range from shortness of breath with exertion, chest pain, and cough to acute respiratory failure. Standard 2-view chest radiographs provide the most useful information, including the degree

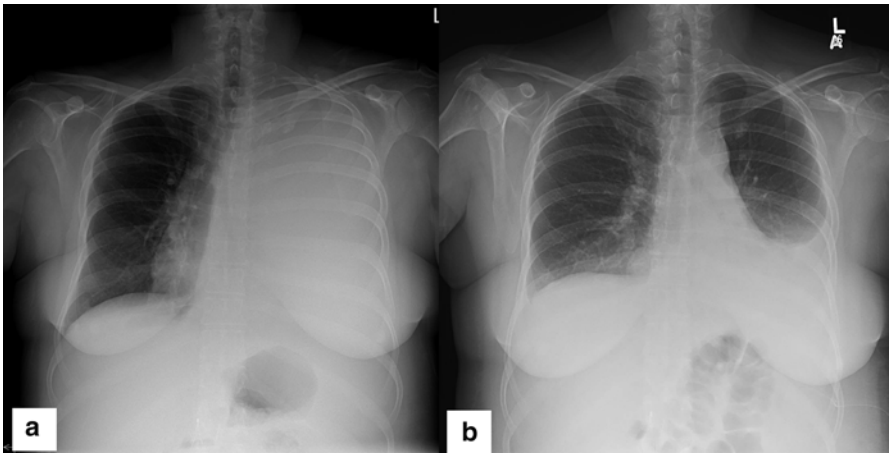

Fig. 4.2 (**a**) Chest radiograph of a 48-year-old woman with metastatic endometrial cancer demonstrating left hemithorax opacification. Of note is a shift of the trachea to the right owing to massive pleural effusion. (**b**) Chest radiograph showing subsequent improvement in aeration of the left hemithorax in the patient after placement of a pleural catheter

of hemithorax opacification, mediastinal shift, and other pulmonary processes (Fig. 4.2). Lateral decubitus films may help identify free-flowing pleural fluid collection. However, bedside ultrasound is used more frequently for this. A CT scan may provide additional information, including that on pleural thickening, loculation, a concomitant mass or endobronchial obstruction, thromboembolic disease, and pneumonia.

Emergent thoracentesis is often required when the patient has a contralateral shift in the mediastinum and/or respiratory distress. Thoracentesis may not relieve respiratory symptoms when the patient has a concomitant respiratory process such as an airway obstruction, a space-occupying mass, lymphangitic spread, a pulmonary embolism, or an infection.

Although the majority of malignant pleural effusions are exudative, 2–5 % of them may be transudative. Pleural fluid should be submitted for cell counts with differentials, chemistry analysis (glucose, protein, lactate dehydrogenase, cholesterol, triglyceride, and hematocrit measurement), and cytology. Also, flow cytometry data may be obtained for patients with underlying hematologic malignancies. Diagnostic thoracentesis is recommended for a new or persistent pleural effusion without a clear etiology (Fig. 4.3).

Therapeutic options for pleural effusion include repeat thoracentesis, placement of an indwelling tunneled pleural catheter, use of a chest tube with talc pleurodesis, and medical thoracoscopy (Fig. 4.4) or video-assisted thoracic surgery with talc pleurodesis.

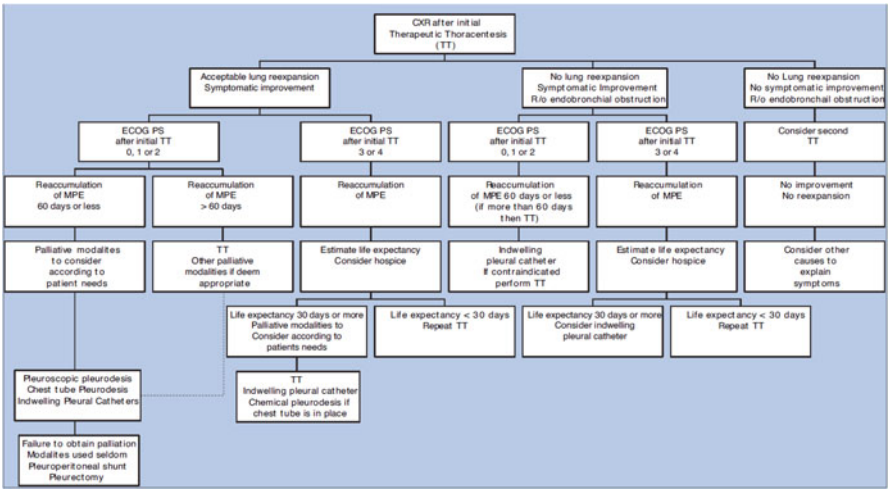

Fig. 4.3 Management of malignant pleural effusions. [Taken from Shannon VR et al. Respiratory complications. Chapter 131 in: *Cancer Medicine*, 8th edition. Hong WK, Bast RC Jr, Hait WN, Kufe DW, Pollock RE, Weichselbaum RR, Holland JF, Frei E III, eds. Shelton, CT: PMPH-USA, LTD. Used with permission from the People's Publishing House-USA.]

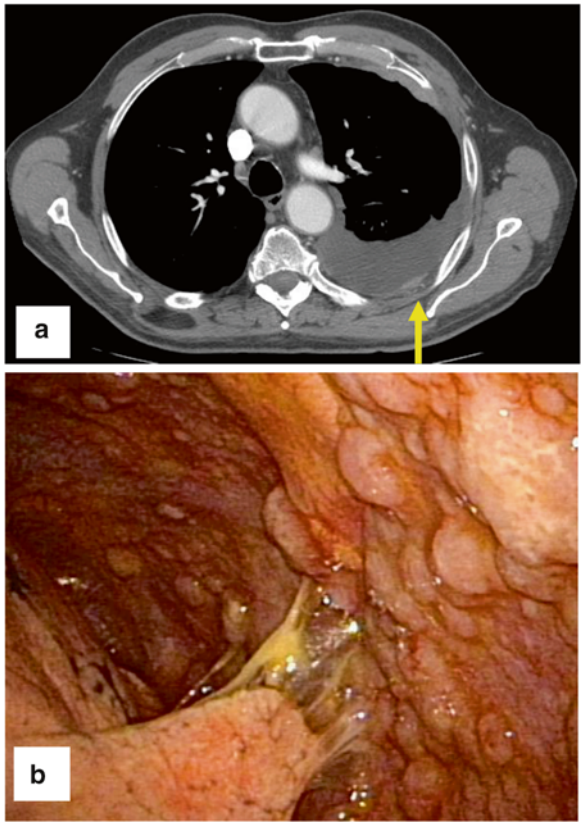

Fig. 4.4 An 83-year-old patient presented with a recurrent exudative pleural effusion of unclear etiology. (**a**) CT scan revealing the pleural effusion with nodularity in the pleura (*yellow arrow*). Ultrasonography revealed a moderate collection of pleural effusions with an atelectatic lung. (**b**) Pleuroscopic image revealing metastatic tumor deposits throughout the pleura consistent with mesothelioma

Thoracentesis

Thoracentesis is the preferred method of diagnosis of a new pleural effusion. Ultrasonographic guidance is almost always used, and it has become the standard of care. Repeat thoracentesis is often recommended for patients with recurrent effusions, which are those recurring at least 60 days after the first pleural procedure; life expectancies shorter than 1 month; and poor performance status. Although the effects of thoracentesis may only be temporary, added discomfort or morbidity resulting from more aggressive procedures may make those procedures less desirable than thoracentesis given the clinical scenario. The American Thoracic Society suggests removal of up to 1.5 L of fluid at a time or until symptomatic.

Indwelling Tunneled Pleural Catheter

Indwelling tunneled pleural catheters may be placed in patients with recurrent (often malignant) pleural effusion (Fig. 4.5). These catheters may be placed in the outpatient or inpatient setting. The care of the catheter is usually performed by patients' family members and/or home health services. Catheters are typically drained daily or 3 times a week until pleurodesis is achieved. The catheter is usually

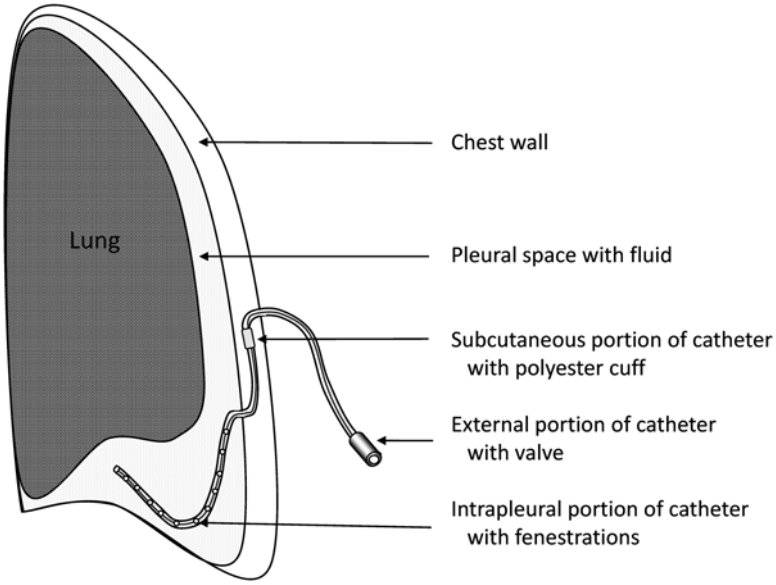

Fig. 4.5 Diagram of an indwelling pleural catheter [Courtesy of Dr. Rodolfo Morice, MD Anderson]

placed anteriorly; however, the placement may vary in patients with loculated fluid or chest wall deformities. Local anesthesia with two incisions (pleural and tunnel entry sites) is part of the catheter placement procedure. The complication rate for tunneled indwelling pleural catheters ranges from 2.0 % to 9.1 %, and complications include bleeding, cellulitis, empyema, catheter malfunction or blockage, chest pain, pneumothorax, and tract metastasis. A pleural catheter may be placed while the patient is receiving chemotherapy; with patient and family education, this is a reasonably safe option.

Pleurodesis with Chest Tube and Thoracoscopic Interventions

A tube thoracostomy is placed with or without sedation, and an inpatient stay is necessary for instillation of sclerosing agents. Medical thoracoscopy involves advancing a pleuroscope into the pleural space under sedation for diagnostic sampling of the pleura and/or instillation of sclerosing agents. Complications of tube thoracostomies include subcutaneous emphysema, fever, pain, sepsis, bleeding, and shock, but they are rarely reported. Video-assisted thoracic surgery is performed in the operating room, and it allows for the use of more extensive therapies. Chemical pleurodesis may result in fever and pain, which may prolong hospitalization. Also, authors have reported acute respiratory failure in patients with tube thoracostomies. Talc is the agent most commonly used with thoracostomies; doxycycline, bleomycin, and other experimental agents also have been used.

In summary, the diagnostic and therapeutic regimens for pleural effusion vary based on patient symptoms, the underlying malignancy, and concomitant pulmonary issues. The approach to definitive management of pleural effusion is based on the cancer stage, the prognosis, patient preference, available resources, and the site of care.

Radiation-Induced Lung Injury

Radiation therapy for cancer is effective because it destroys cancer cells, but it can be equally, if not more, damaging to adjacent normal tissue. Pneumonitis is a well-recognized potential complication of irradiation of the thoracic area (Graves et al. 2010). Damage to pneumocytes and endothelial cells may cause acute inflammation, and chronic injury reflects the resulting interstitial fibrosis.

The amount of ionizing radiation required to cause pneumonitis is about 20–25 Gy, whereas the intent-to-cure dose is considerably higher. An important consideration is the planned schedule for radiation administration. For example, daily treatments of 2.67 Gy carry significant risk, whereas fractions of 1.8–2.0 Gy are better tolerated. The total dose and volume of irradiated lung are obviously important, but other variables, including previous radiation therapy, individual

genetic susceptibility, and underlying chronic lung disease, should be taken into consideration. Certain chemotherapeutic agents (e.g., bleomycin, vincristine, doxorubicin, cyclophosphamide, actinomycin D, gemcitabine, taxanes) may predispose patients to radiation pneumonitis, which may occur as early as 6 weeks and up to 1 year after radiation therapy. Both acute and chronic radiation pneumonitis may be insidious in development and may unfold in a continuous, sequential fashion.

The acute phase of radiation pneumonitis is characterized by nonproductive cough in its mildest form. With increasing severity, the cough becomes refractory, dyspnea becomes more pronounced, and oxygen therapy for hypoxia may become necessary. Fever may be present, as well. Radiologic findings include diffuse haze and indistinct vascular margins with sharp cut-off from surrounding unaffected tissue. A radiographically diffuse pattern outside the irradiated field of the lung develops, indicating a hypersensitivity-like reaction. A well-recognized rare presentation is radiation recall pneumonitis, which develops upon challenge with medications such as anthracyclines, taxanes, tamoxifen, and gemcitabine. The radiation therapy may have been complete weeks to months prior to challenge.

Corticosteroids may be used for radiation pneumonitis and tapered as determined by the clinical response. Treatment of very late-stage disease with steroids has demonstrated no significant clinical benefits. Researchers developed intensity-modulated radiation therapy and proton therapy to reduce the irradiation of normal tissue, but radiation pneumonitis can still occur in patients who undergo these two modalities. Pharmacologic therapy with amifostine has some cytoprotective properties.

Aspiration Pneumonia

Swallowing dysfunction in cancer patients can be caused by the underlying malignancy or its treatment. Any disturbance in the swallowing mechanism involving the central or muscular phase can result in aspiration of oropharyngeal contents into the lung.

Aspiration can lead to pneumonitis or pneumonia in the acute or chronic phase. Aspiration pneumonia may be overt or silent, and it often mimics community- or hospital-acquired pneumonia. Malignancies of the head and neck, esophagus, and lung often predispose patients to aspiration pneumonia. Tumor site, age, chemoradiation with mucositis, strictures, and surgery-related complications such as denervation, scar tissue formation, and reconstruction are factors affecting the development of aspiration pneumonia (Raber-Durlacher et al. 2012). Primary brain tumors and metastatic brain lesions can cause aspiration pneumonia via a centrally mediated mechanism.

If aspiration is severe enough to cause respiratory failure, it can be fatal. Pneumonia and pneumonitis lead to cough with or without fever. When examining patients' medical histories, physicians should focus on their oncologic histories, presence of cough after swallowing meal boluses, sensation of dysphagia, perception of excessive viscous or paucity of saliva, examination findings revealing poor

dentition making patients prone to infection, and complaints of nausea with or without vomiting. A modified barium swallow is the gold standard for evaluation of dysphagia and is performed with ingestion of measured quantities of liquids and solids. Fiber-optic endoscopic evaluation of swallowing is an alternative method of examination of residuals, laryngeal penetration, and aspiration.

Cultures often reveal oropharyngeal flora with aerobic and anaerobic bacteria in patients with aspiration pneumonia, and antimicrobial treatment aimed at these pathogens is usually effective. Definitive treatment of aspiration pneumonia involves prevention of future aspiration episodes using swallowing exercises, feeding gastrostomies, or esophageal stricture correction. Prevention of dysphagia may involve changes in dosing and delivery of radiation, close adherence to recommendations for early postradiation swallowing recovery (Rosenthal et al. 2006), use of cytoprotectants, and reconstructive surgery with tumor resection.

Hemoptysis

Hemoptysis may occur in cancer patients, mainly owing to the underlying malignancy or metastatic disease or as a complication of therapy (Shannon et al. 2010b). Massive hemoptysis carries a high mortality rate, and death generally results from asphyxiation rather than blood loss. In quantitative terms, massive hemoptysis is described as loss of at least 600 mL of blood in a 24-hour period.

Bleeding from a pulmonary malignancy can be caused by endobronchial disease or lesions distal to the airway. Bronchiectasis, invasive pulmonary infections (such as those with *Aspergillus* species), thromboembolic disease, and arteriovenous malformations are other possible etiologies of hemoptysis. Chemotherapy with agents that affect coagulation parameters and platelets (e.g., bevacizumab) may also predispose patients to bleeding. Diffuse alveolar hemorrhage may occur in patients after bone marrow transplantation and in leukemia patients with refractory thrombocytopenia. These patients may also present with hemoptysis. Treatment of hemoptysis in this subset of patients includes optimization of hematologic parameters and empiric steroids.

The degree and severity of hemoptysis direct management strategies for it. Supportive treatment, including airway management, oxygenation, and assessment of the transfusion requirement, starts as soon as the patient presents. A CT scan should be performed to review the lung parenchyma, pleural space, and tracheobronchial disease. Acute management should include monitoring of hemoglobin levels and hematocrit, transfer to a higher level of care, and, if breathing worsens, double-lumen intubation with ventilation of the side without bleeding. Also, positioning of the patient in the decubitus position (for the side that is bleeding) can help protect the contralateral lung.

Endobronchial bleeding may be controlled with bronchoscopy and interventional techniques such as cauterization (argon cautery, laser cautery, or electrocautery). Cold saline and local epinephrine administered in the airway with a bronchoscope

wedged at the site of bleeding may also help. Other interventions, such as a Fogarty balloon catheter, can be used and left in place for 24–48 h for a tamponade effect. In most cases of hemoptysis with significant endobronchial disease, rigid bronchoscopy is advised for maintenance of improved control of the airway. In cases without endobronchial bleeding, arteriography of the bronchial vessels may permit embolization with a high success rate. Often, bronchoscopy will help identify where the bleeding is originating from; frequently, a source may be suspected and subsequently embolized (Wang et al. 2009). Care is taken to avoid injecting the anterior spinal artery, which arises from a bronchial artery in 5 % of humans. Definitive therapy involves treatment of the underlying disease, external irradiation, or endobronchial brachytherapy. In some cases, surgical resection may be recommended.

Malignant Airway Obstruction

Malignant airway obstruction may involve direct extension of a tumor, such as a bronchogenic carcinoma, or it may be primarily an endobronchial lesion, such as a carcinoid tumor. The obstruction may be central or peripheral; focal or diffuse; and endoluminal, extraluminal, or a combination of the two. Also, extrinsic compression of the airway owing to a tumor or lymphadenopathy can compromise the tracheobronchial tree. The location and extent of the obstruction contributes to the patient's symptomatology and directs therapeutic interventions for it. Patients may be asymptomatic or have symptoms ranging from frank uncontrolled hemoptysis to respiratory failure. Specifically, symptoms include shortness of breath, wheezing, stridor, hemoptysis, cough, recurrent respiratory infections, and chest discomfort. Stridor is usually pathognomonic of a significant tracheal obstruction. Airway obstruction leads to disturbance of flow dynamics, cellular response, and blood flow. Direct extension of tumors destroys normal barriers, leading to seepage of blood (hemoptysis) and compromise of the airway. Primary airway tumors are difficult to diagnose, as patients with them have mild to moderate symptomatology over prolonged periods before diagnosis. Authors have reported unexplained dyspnea upon exertion, wheezing, stridor, and longstanding cough in these patients. Mucus production is a predominant symptom related to extrinsic compression, especially in lower airways. This results in distal obstructive accumulation of debris causing bacterial overgrowth and infection. The most severe cases of airway obstruction are those with massive hemoptysis and airway compromise causing respiratory failure. Other comorbid conditions, such as chronic lung disease, pleural effusion, and bronchospasm, may lead to rapid decompensation and respiratory insufficiency.

Respiratory symptoms usually precipitate a chest radiograph, which can provide information such as whether an infiltrate (postobstructive pneumonia, mass) or deviation or compression of the trachea is present. A more thorough evaluation using CT with and without contrast provides a view of the tracheobronchial tree and lymph nodes. Occasionally, pulmonary function tests are performed and may reveal

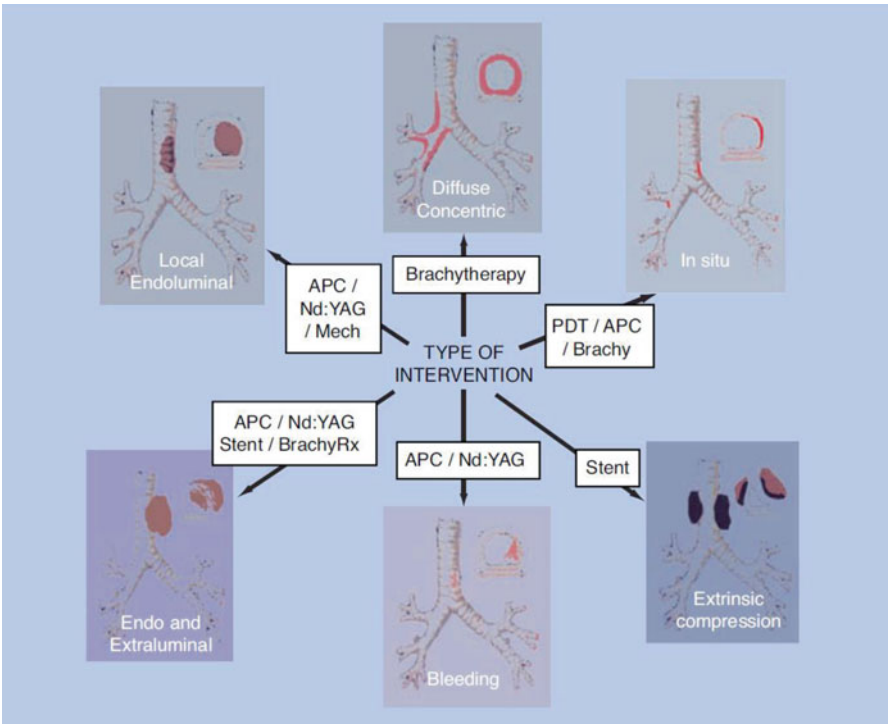

Fig. 4.6 Interventional bronchoscopic therapy for airway obstructions. *APC* argon plasma coagulation, *Nd:YAG* neodymium-doped yttrium aluminum garnet, *Mech* mechanical ventilation, *PDT* photodynamic therapy, *Brachy* brachytherapy, *BrachyRx* brachytherapy. [Taken from Shannon VR et al. Respiratory complications. Chapter 131 in: *Cancer Medicine*, 8th edition. Hong WK, Bast RC Jr, Hait WN, Kufe DW, Pollock RE, Weichselbaum RR, Holland JF, Frei E III, eds. Shelton, CT: PMPH-USA, LTD. Used with permission from the People's Publishing House-USA.]

flattening of the flow-volume loop, suggesting an intrathoracic or extrathoracic obstruction. Definitive evaluation requires bronchoscopy to evaluate the tracheobronchial tree. Patients with significant hemoptysis and/or airway compromise likely need a rigid bronchoscopy.

Interventions for airway obstructions are determined by the patient's extent of disease and symptoms. Possible interventions are shown in Fig. 4.6 (Shannon et al. 2010b). Certain situations may necessitate the use of two procedures: a diagnostic bronchoscopy followed by therapy. Diagnosis of a malignancy via sampling of lymph nodes or lung tissue also may be required at the time of bronchoscopy. Although many interventions can be performed using flexible bronchoscopy, a more controlled procedure using rigid bronchoscopy may be warranted. The clinical situation can help determine the urgency of the procedures. For example, airway compromise with stridor and hypoxemia owing to compression of the upper airway may necessitate an emergent tracheostomy. Respiratory failure may require stabilization via noninvasive positive pressure ventilation and/or elective endotracheal

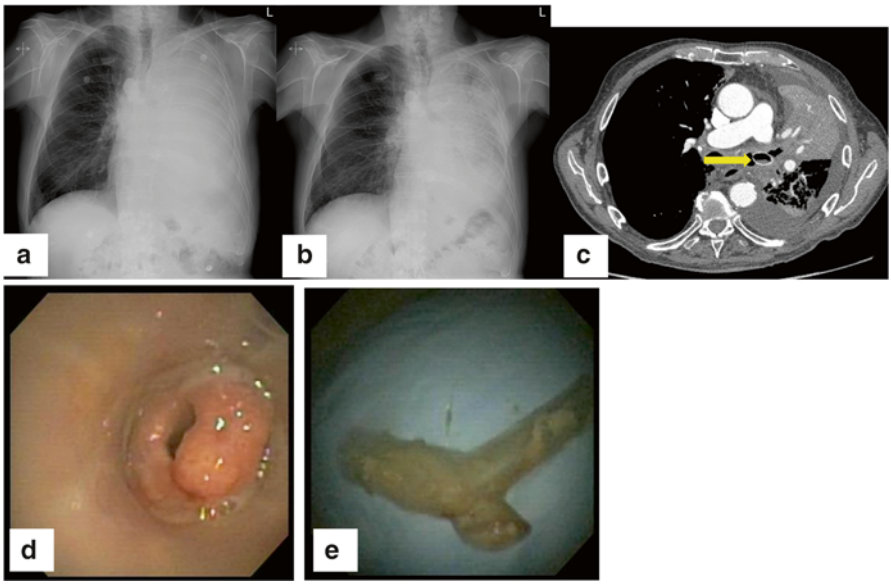

Fig. 4.7 An 80-year-old man with non-small cell lung cancer initially presented with a left mainstem endobronchial tumor and underwent debulking and placement of a tracheobronchial Y stent. (**a**) Chest radiograph of the patient 6 months after radiation therapy demonstrating left hemithorax opacification (of note is the position of the trachea). (**b**) Another chest radiograph of the patient after ultrasound-guided thoracentesis of the left hemithorax demonstrating somewhat improved aeration (of note is a shift of the trachea to the left, suggesting volume loss). (**c**) CT scan of the patient revealing an obstruction in the stent (*yellow arrow*). (**d**) Bronchoscopic evaluation revealing occlusion of the stent with thick mucus, granulated tissue around the stent, and possible recurrence of endobronchial disease. (**e**) A mucus cast aspirated by the patient after diagnostic specimens were obtained from him. [Courtesy of Dr. George A. Eapen, MD Anderson.]

intubation. Also, uncontrolled hemoptysis may require placement of a double-lumen endotracheal tube to protect the unaffected lung. Physicians with specialized training, such as interventional pulmonologists and thoracic surgeons, often perform such airway interventions.

These procedures have both risks and benefits. For example, placement of stents may improve or temporize symptoms so that the patient can receive treatment. However, stents may be associated with complications, including infection, stent migration, and granulated tissue formation (Fig. 4.7) (Ost et al. 2012). In certain cases, airway intervention is not possible. For instance, hemoptysis without an identifiable central lesion may indicate bleeding from distal lung parenchyma. If the bleeding is persistent and significant, irradiation, bronchial artery embolization, and/or surgical intervention is recommended. In cases of distal disease, stent placement is not indicated, as airflow to a damaged lung will not improve respiratory symptoms. Surgery is the long-term solution if an airway obstruction is resectable, but often, chemotherapy and/or radiation therapy is indicated.

Pulmonary Vascular Disease

With the exception of pulmonary thromboembolic disease, pulmonary vascular disease in cancer patients has not been well described. Under the updated clinical classification of pulmonary hypertension (PH) at the 4th World Symposium on PH, hematologic disorders and other cancer-related conditions are categorized as group 5 PH, or PH with unclear multifactorial mechanisms (Simonneau et al. 2009). Authors have reported PH in patients with chronic myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, and chronic myeloid leukemia. Authors also have described it in patients with tumor obstruction (most commonly pulmonary artery sarcoma), occlusion of microvasculature by metastatic tumor emboli, and mediastinal fibrosis. Patients with tumor emboli may present with rapidly progressive PH and abrupt onset of dyspnea that rapidly progresses to sudden cardiovascular collapse and death. CT will not reveal proximal thrombi, but it often shows thickening of septa. Ventilation perfusion scans are generally abnormal, with multiple subsegmental perfusion defects. The majority of reported cases of pulmonary vascular disease have been associated with breast, lung, and gastric carcinomas (Shannon et al. 2010b). Pulmonary vascular disease is most often diagnosed at necropsy, and definitive treatment of it has yet to be identified. Treatment with dasatinib, a tyrosine kinase inhibitor, has induced severe precapillary PH, with improvement in it usually observed after withdrawal of the medication (Montani et al. 2012).

Cancer patients who present with unexplained dyspnea or elevated right ventricular pressure should first undergo testing to exclude thromboembolic disease. Noninvasive screening for PH typically includes transthoracic Doppler echocardiography, which provides an estimation of the pulmonary artery systolic pressure. Cardiac dysfunction, body habitus, untreated obstructive sleep apnea, and chronic lung disease may influence pulmonary artery systolic pressure according to echocardiography. In cases with a high index of suspicion for PH, right heart catheterization is recommended to confirm the diagnosis, assess associated hemodynamic impairments (e.g., right atrial pressure, pulmonary capillary wedge pressure), and evaluate the vasoreactivity of the pulmonary circulation.

PH is defined as a mean pulmonary artery pressure of at least 25 mm Hg, and right heart catheterization is required to confirm PH. The various available therapies for PH have not been well studied in cancer patients. Close monitoring of symptoms and functional status by a PH specialist is recommended, and referral to a specialized center may be warranted.

Perioperative Pulmonary Issues

Surgery for an anatomically resectable tumor may affect respiratory function. The approach to assessment of patients with such tumors involves determination of their functional operability and predicted long-term pulmonary disability

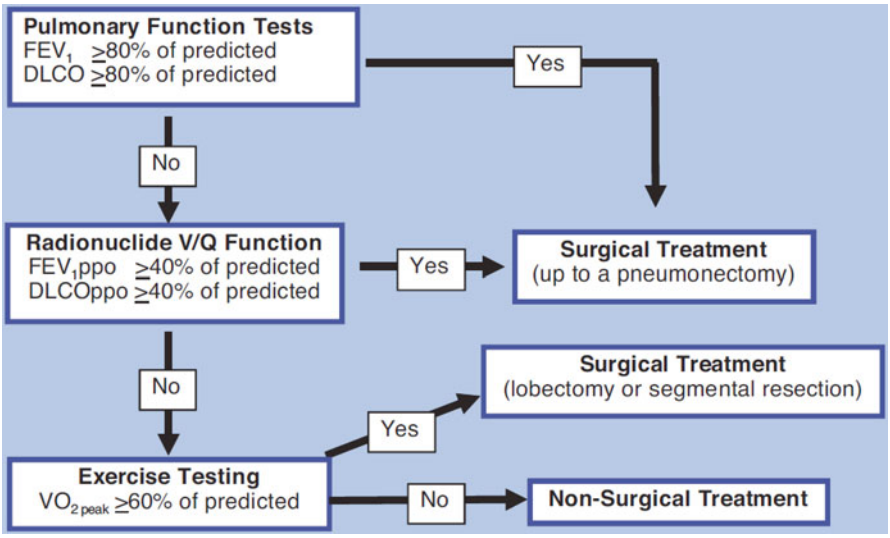

Fig. 4.8 Approach to preoperative evaluation for lung resection. *FEV_1* forced expiratory volume in 1 s, *DLCO* diffusing capacity, *FEV_1ppo* predicted postoperative forced expiratory volume in 1 s, *DLCOppo* predicted postoperative diffusing capacity, *VO_2* oxygen consumption. [Reprinted from Baser S, Shannon VR, Eapen GA, et al. Pulmonary dysfunction as a major cause of inoperability among patients with non-small-cell lung cancer. Clin Lung Cancer. 2006;7(5):344–349. With permission from Elsevier.]

following surgery. Optimization of comorbidities and pulmonary-specific testing is recommended. Our approach to lung resection is summarized in Fig. 4.8. The first step includes measurement of baseline pulmonary function and quantitative radionuclide regional ventilation-perfusion pulmonary studies to measure postoperative lung function. If the results of these studies are borderline, cardiopulmonary exercise testing may be performed (Walsh et al. 1994). Given its risks and benefits, the final decision regarding surgery should be made by the patient and the surgeon.

Preoperative evaluation of cancer patients is important. Recognition and treatment of underlying chronic lung disease or heart failure may impact the perioperative period. Postoperative pulmonary complications may include atelectasis, infection, aspiration, prolonged mechanical ventilation and respiratory failure, exacerbation of underlying chronic lung disease, and bronchospasm. Postoperative pulmonary complications may be greatly affected by the site and duration of the surgery and type of anesthesia and neuromuscular blockade. Interventions in the postoperative period include oxygen therapy, bronchodilator administration, and positive pressure therapy. Diuretics, steroids, and antimicrobial therapy should be given according to clinical judgment.

Undiagnosed obstructive sleep apnea is a frequent cause of critical respiratory events, including hypoxemia and unplanned reintubation, immediately after

surgery. Screening patients for obstructive sleep apnea based on symptoms (snoring, witnessed apnea, gasping/choking arousal at night, and daytime hypersomnia) or clinical features (obesity and crowded oropharynx) may help alter perioperative management of it. Use of perioperative positive pressure ventilation may be warranted, and caution against excessive sedation and/or analgesia is recommended. Follow-up with a sleep specialist and subsequent polysomnography are advised.

Pulmonary Complications Associated with Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is the infusion of multipotent hematopoietic stem cells, usually derived from bone marrow, growth factor-stimulated peripheral blood, or cord blood. HSCT is further categorized based on the origin of the stem cells: autologous (from the patient), syngeneic (from an identical twin of the patient), or allogeneic (an individual not related to the patient). The main indication for HSCT is treatment of a hematologic malignancy. Prior to stem cell infusion, high-dose chemotherapy with or without total-body irradiation is administered as a conditioning regimen. This is done primarily to ablate the bone marrow, maximize killing of tumor cells, and induce immunosuppression to prevent rejection of the donor cells (Kotloff et al. 2004). Patients are monitored closely during and after stem cell infusion for engraftment, respiratory issues, and graft-versus-host disease.

Authors have reported a variety of pulmonary complications, both infectious and noninfectious, in patients who undergo HSCT, and an estimated 60 % of patients who receive these transplants may have respiratory issues. Pulmonary complications are classified as early (fewer than 100 days after transplantation) or late (100 days or more after transplantation). The timing of HSCT may help in terms of diagnosis, as specific complications tend to occur within well-defined periods (Kotloff et al. 2004). Although pneumonia may occur at any time after transplantation, bacterial, fungal, and viral pathogens are most often found in the pre-engraftment period in the presence of profound neutropenia. Infectious complications are more common in patients who undergo allogeneic HCST than in those who undergo autologous or syngeneic HSCT because they are administered immunosuppressive agents to prevent or delay graft-versus-host disease. Prompt evaluation with bronchoalveolar lavage may help identify opportunistic organisms and differentiate infectious and noninfectious etiologies (Shannon et al. 2010a). Early noninfectious pulmonary complications include pulmonary edema, idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, and engraftment syndrome. Treatment is usually supportive, including empiric antimicrobial therapy, oxygen therapy, and diuresis, and physicians have used empiric corticosteroids in cases with diffuse alveolar hemorrhage or engraftment syndrome. Late noninfectious pulmonary com-

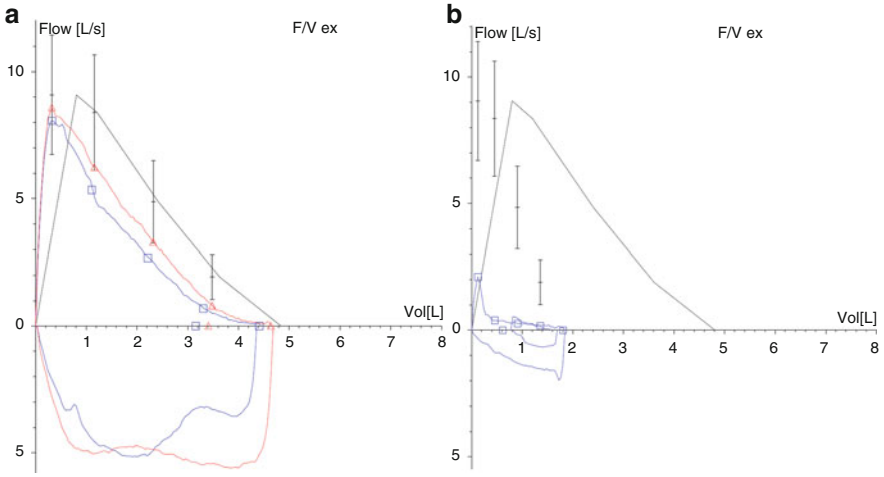

Fig. 4.9 A 51-year-old man with chronic myeloid leukemia experienced worsening dyspnea 9 months after transplantation of stem cells from a matched unrelated donor and was diagnosed with posttransplantation constrictive bronchiolitis. (**a**) Pretransplantation pulmonary function test revealing a mild obstruction without significant bronchodilator response (*red line*). (**b**) Posttransplantation pulmonary function test revealing a severe airflow obstruction

plications include posttransplantation constrictive bronchiolitis, pulmonary veno-occlusive disease, and posttransplantation lymphoproliferative disorder.

Posttransplantation constrictive bronchiolitis is the most common late complication of allogeneic HCST. It is representative of chronic graft-versus-host disease of the lung and characterized by insidious onset of severe airflow obstruction, which leads to progressive respiratory insufficiency and even death (Fig. 4.9). High-resolution CT often demonstrates a mosaic pattern with air trapping, and pulmonary function tests demonstrate severe airflow obstruction. Treatment includes augmentation of systemic immunosuppression using corticosteroids and inhalation of high-dose corticosteroids (Bashoura et al. 2008). Lung transplantation may be an option for select patients.

Diaphragmatic Dysfunction

Diaphragmatic dysfunction also should be considered in the differential diagnosis of dyspnea in cancer patients. Diaphragmatic weakness or paralysis often results from injury to the phrenic nerve, especially after surgery or owing to compression by a bronchogenic or mediastinal tumor (McCool and Tzelepis 2012). Other etiologies

include trauma, metabolic disturbances, infections, and inflammatory disorders. Diaphragmatic dysfunction may be unilateral or bilateral. Patients with unilateral dysfunction are usually asymptomatic at rest but may have dyspnea under exertion. Patients with bilateral diaphragmatic dysfunction often have more symptoms, with unexplained dyspnea or recurrent respiratory failure. Initial diagnostic testing includes chest radiography (elevated hemidiaphragm), fluoroscopy (sniff test, paralysis of hemidiaphragm with inspiration), and pulmonary function tests (decreased total lung capacity consistent with restriction).

Treatment of diaphragmatic dysfunction is guided by the underlying etiology, the presence or absence of symptoms, and nocturnal hypoventilation. Overnight polysomnography confirms sleep-related hypoventilation, and noninvasive positive pressure ventilation is recommended for treatment of sleep-disordered breathing. Co-existing conditions such as obesity, weakness of other muscle groups, and underlying cardiopulmonary disease may exacerbate symptoms related to diaphragmatic dysfunction. In addition, new parenchymal infiltrates owing to infection, pneumonitis, or malignancy may acutely contribute to these symptoms. Noninvasive positive pressure ventilation is useful in patients with respiratory insufficiency.

Pulmonary Rehabilitation

Pulmonary rehabilitation is an evidence-based, multidisciplinary, comprehensive intervention for chronic lung disease. It is often tailored to the patient and his or her underlying disease with the intent of reducing symptoms, optimizing functional status, increasing participation, and ultimately, reducing health care costs. The primary goals of pulmonary rehabilitation include lower and upper extremity exercise conditioning, breathing retraining, education, and psychosocial support. Other therapeutic modalities, such as smoking cessation, oxygen therapy, bronchodilators, antibiotics, nutritional support, and respiratory muscle training and resting, are often stressed.

Pulmonary rehabilitation has proven beneficial in patients with chronic obstructive pulmonary disease and recipients of lung transplants by improving dyspnea and fatigue, but its role in patients with cancer remains to be defined. Several reports have suggested that pulmonary rehabilitation counters chemotherapy-related fatigue, improves performance status, and reduces the length and frequency of hospitalization in patients with cancer (Shannon et al. 2010b). Small studies of pulmonary rehabilitation in the perioperative period in patients undergoing surgery for lung cancer demonstrated improvement of symptoms (Shannon 2010). Also, authors reported that pulmonary dysfunction is a major cause of inoperability in patients with non-small cell lung cancer (Baser et al. 2006). Pulmonary rehabilitation may be a crucial treatment in such patients, and prospective studies of it are ongoing.

Key Practice Points

- Sensation of shortness of breath in cancer patients requires a systematic management approach that should include differential diagnosis that is cancer-specific or treatment-related.
- Thoracentesis is increasingly done using ultrasonographic guidance and is the diagnostic test of choice for new-onset pleural effusion.
- Use of indwelling pleural catheters is safe and effective in the management of malignant pleural effusions.
- Radiation-induced lung injury may occur 6 weeks to 1 year after radiation therapy.
- Rigid bronchoscopy with endobronchial management or bronchial embolization helps control acute hemoptysis in the majority of cancer patients.
- Malignant airway obstruction symptomatology depends on the location and extent of disease and directs possible therapeutic interventions.
- Diaphragmatic weakness or paralysis often results from injury to the phrenic nerve, especially after surgery or owing to compression by bronchogenic and mediastinal tumors.
- Posttransplantation constrictive bronchiolitis is the most common late pulmonary complication in patients who undergo allogeneic HCST and is representative of graft-versus-host disease of the lung.

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Chapter 5
Gastrointestinal Emergencies in the Oncology Patient

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Chapter Overview

A large number of cancer patients present with gastrointestinal (GI) complaints owing to either the disease process or complications of treatment. Nausea and vomiting occur frequently and require prompt intervention to avoid dehydration, delays in treatment, and lack of compliance. Different diagnostic considerations must be kept in mind, including chemoradiation, obstruction at any level of the GI tract, brain metastasis, and metabolic causes. Diarrhea is encountered frequently and may be related to infection, chemotherapy, radiation therapy, graft-versus-host disease (GVHD), secretory tumors, or neutropenia in the cancer patient. In addition, malignant bowel obstruction (MBO) is common in patients with intra-abdominal or extra-abdominal malignancies. Treatment of such obstructions varies according to the etiology and patient's performance status. The different modalities of therapy for them are discussed in this chapter. GI bleeding, hepatobiliary problems such as acute cholangitis, spontaneous bacterial peritonitis, ascites, and their treatment in cancer patients are also described. Recognizing, establishing an accurate diagnosis of, and promptly intervening for these clinical situations once a physician is presented with them is of paramount importance, as they may significantly affect the patient's survival.

Introduction

Most patients with cancer incur GI complications over the course of their disease. This may result from the disease itself or its treatment, and these complications may be emergent. Symptomatic relief of nausea, vomiting, anorexia, or constipation can bring valuable relief from suffering, whereas some problems, such as cholangitis,

bleeding, and bowel obstruction, may be life-threatening. This chapter reviews these conditions and their management.

Nausea and Vomiting

Nausea is a very disagreeable symptom even when unaccompanied by vomiting and can cause noncompliance. A common misconception is that the advent of new antiemetics in the 1980s eliminated the problem of nausea and vomiting in the cancer patient receiving chemotherapy.

The genesis of nausea and vomiting has different etiologies in the cancer patient, including but not limited to chemotherapy; radiation therapy; the cancer itself; bowel obstruction; metabolic upset such as hypercalcemia, hyperglycemia, and uremia; and infections such as gastroenteritis. Gastroparesis secondary to cancer, chemotherapy, or diabetes should be considered. A thorough history and physical examination will clarify the possibilities and direct work-up. Special consideration should be given to the possibility of vestibular dysfunction and brain metastasis in patients with intractable nausea and vomiting.

Radiation therapy may be responsible for nausea and vomiting depending on the site, dosage, and fractionation schedule. These complications are expected in patients undergoing total body, half-body, or abdominal irradiation and are even more likely in those receiving concomitant chemotherapy.

Chemotherapy-induced nausea is subdivided into acute, delayed, and anticipatory categories. Acute onset occurs within 2 h, peaks at 4–6 h, and resolves by 24 h. Delayed onset occurs after 24 h and may persist for days. Certain agents, such as cisplatin, carboplatin, cyclophosphamide, and doxorubicin, are especially potent in this regard.

Anticipatory nausea is caused by a conditioned reflex (Pavlovian conditioning). It is said to be more common in female and younger patients than in male and older ones. Curiously, heavy alcohol consumption lowers susceptibility to this type of nausea. Previous chemotherapy-related nausea is the most potent predisposing factor. Prophylaxis for nausea is the best way to prevent it.

Although the dosage and rate and route of administration of a chemotherapeutic drug are important factors, the inherent emetogenic potential of the agent best predicts nausea. The National Comprehensive Cancer Network classifies agents into high, moderate, low, and minimal risk categories with corresponding emesis prevention protocols (Ettinger et al. 2012).

Complications of nausea and vomiting include dehydration, electrolyte imbalance, and weight loss. Nausea in the cancer patient may be caused by medications other than those used in chemotherapy, such as opiates, digoxin, and many others. The emetic reflex is located in the nucleus tractus solitarius in the brain stem and the chemoreceptor trigger zone in the floor of the fourth ventricle. Circulating chemicals stimulate the chemoreceptor trigger zone, which in turn activates the vomiting center, which also receives afferents from the cerebral cortex, vestibular apparatus, and GI tract via the splanchnic tracts and vagus nerve.

Treatment

A variety of agents are available for treatment of nausea. The 5-HT_3 antagonists, which were introduced in the 1980s, are very efficacious. Side effects of these agents are acceptable and include headache, asthenia, constipation, and dizziness. Overall, the 5-HT_3 antagonists are equally effective, although clinical experience suggests that one may work in a patient in whom the others do not. Researchers have demonstrated the efficacy of palonosetron in particular in the prevention of delayed nausea in several multicenter, randomized, double-blind phase 3 trials (Aapro 2007; Yang and Scott 2009).

Aprepitant, a neurokinin-1 receptor inhibitor, has exhibited efficacy in the control of delayed nausea when given as a single agent. It also decreases the incidence of acute and delayed nausea and vomiting when used in conjunction with dexamethasone and a 5-HT_3 antagonist.

Targeting the different receptors involved in the genesis of nausea is the rationale behind concomitant use of different agents. In addition to serotonin antagonists and steroids, the most frequently used medications in treatment of nausea and vomiting include dopamine receptor antagonists, antipsychotics, phenothiazines, benzodiazepines, and, occasionally, cannabinoids. The use of acupuncture and behavioral therapy may play an important role in nausea treatment in a subset of patients (Ezzo et al. 2006).

In summary, prevention of nausea and vomiting is paramount in cancer patients. The patients must be supported throughout the emetogenic period. Oral and intravenous (IV) routes of serotonin antagonist administration have been equally effective. Physicians are recommended to select an agent and administer it on a predetermined schedule rather than as needed. They also should consider adding an antiemetic from a different drug class for symptom control as well as different agents concomitantly, alternating schedules and routes.

Constipation

Constipation is a particularly common complaint of cancer patients, and relief of it can provide much comfort. It is usually multifactorial in its etiology, providing several possibilities for intervention. In most cases, constipation can be anticipated, and effective countermeasures can be implemented.

A careful history will both establish rapport with the patient with constipation and uncover possible causes of it as well as suggest or rule out other diagnoses. The underlying malignancy, a concomitant illness, the timing of the complaint, a medication history including over-the-counter drugs, and associated symptoms such as nausea, vomiting, and abdominal pain will direct further work-up.

Physical examination of the abdomen will detect distension and tenderness, suggesting a condition requiring surgery. In the absence of neutropenia or other

contraindications, hernial orifices and a rectal examination may reveal fecal impaction and bleeding as well as local impairments such as fissures, neoplasms, and thrombosed hemorrhoids. Radiologic evaluation logically follows and includes a flat and upright X-ray of the abdomen and computed tomography (CT) with or without contrast to rule out an obstruction or lesion.

Similarly, clinical findings direct laboratory testing for constipation. The purposes of laboratory evaluation are to rule out another, possibly more immediately threatening condition; confirm the presence and severity of constipation; and suggest the therapeutic approach.

Management of constipation requires attention to fluid intake and electrolyte rebalancing. A dehydrated patient with poor oral intake may need IV replacement. Other therapeutic modalities include stool softeners, osmotic and stimulant laxatives, prostaglandin analogs, enemas, and suppositories. Digital disimpaction may be necessary and remarkably effective and should not be delegated to the unsupervised most junior member of the medical team. In fact, rectal impaction can cause large bowel obstruction with or without overflow incontinence.

Ideal prophylactic measures for constipation include adequate water intake, physical activity, a high-fiber diet, and avoidance of constipating agents. Opioid agonists are inherently constipating via their effect on GI μ-opioid receptors. Cancer patients may be elderly, physically debilitated and immobile, and disinterested in food and may need medications that cause constipation. Additional measures include the use of fiber supplements like methylcellulose, psyllium, and polycarbophil, which are effective for the prevention and reversal of mild constipation. Stool softeners certainly soften the stool, but their ability to evacuate it unaided seems uncertain. Dioctyl calcium sulfosuccinate may be preferable to the sodium equivalent. Stimulant laxatives, such as the anthraquinone senna and the diphenylmethane bisacodyl, are useful on an occasional basis, as they can cause tachyphylaxis. Polyethylene glycol is an osmotic laxative that is well tolerated; 17 g of it in 200 cc of water may be given daily. Lactulose and sorbitol are alternatives, if tolerated. Misoprostol is a prostaglandin E_1 analog that stimulates intestinal motility and is well tolerated at 200 mg given every 2 days (Davila and Bresalier 2008).

μ-opioid GI receptor antagonists such as methylnaltrexone have been effective in patients with advanced disease without reversing analgesia, as they do not cross the blood-brain barrier (Thomas et al. 2008).

Diarrhea

Diarrhea is defined in terms of frequency, consistency, and volume of the stool.

Several mechanisms explain diarrhea in the cancer patient, and evaluation of it can be exhausting and costly if relevant clinical information and likely scenarios are not taken into consideration. Diarrhea can be acute—lasting less than 2 weeks—or chronic—lasting more than 4 weeks. This section focuses on common causes of acute diarrhea in the cancer patient.

Infectious Diarrhea

Predisposing conditions for infectious diarrhea in the cancer patient, particularly those associated with neutropenia, are human immunodeficiency virus infection and bone marrow transplantation. Bone marrow transplant recipients are particularly susceptible to viral infections such as those with cytomegalovirus, herpesvirus, astrovirus, adenovirus, and rotavirus. Bacterial infections include those with *Escherichia coli* 0157 and *Yersinia*, *Salmonella*, *Shigella*, and *Campylobacter* species. Parasites causing diarrhea in this patient population are unusual but should be considered. The most common infecting parasites are *Cryptosporidium* species, *Entamoeba histolytica*, and *Giardia lamblia*.

Clostridium difficile Infection

The most common form of diarrhea in hospitalized patients is caused by *Clostridium difficile* and must be considered for any cancer patient undergoing chemotherapy or receiving antibiotics. Diarrhea caused by this infection may be associated with methotrexate, cyclophosphamide, and doxorubicin use, whereas clindamycin traditionally has been the antibiotic most frequently responsible for it. Also, use of fluoroquinolones and cephalosporins is often involved owing to their widespread use. Antibiotic and chemotherapeutic agents disrupt the intestinal flora and mucosa, favoring *C. difficile* replication and toxin production. *C. difficile* strains vary in their virulence owing to gene mutations as demonstrated in the production of toxins A and B, which are antigenically distinct (Kelly 2009). Age, general condition, and prolonged hospitalization are risk factors for *C. difficile* infection. Furthermore, the hospital environment includes resistant species. Hand washing to reduce the spread of infection therefore must be an integral part of the therapeutic approach in cancer patients.

Clinical manifestations of *C. difficile* infection include profuse diarrhea with a characteristic foul smell, abdominal cramps, fever, ileus, and the presence of pseudomembranous colitis on endoscopic images. Leukocytosisindicated by a white blood cell count greater than 15,000 K/μL, an albumin level less than 2.5 g/dL, admission to the intensive care unit, fever with a temperature of 101 °F or greater, and the presence of pseudomembranous colitis are risk factors. Indicators of infection severity are enzyme immunoassays used to detect the presence of toxins A and B, which are fast, inexpensive, and very specific but lack sensitivity. An infection-negative assay does not supersede a clinical diagnosis. Polymerase chain reaction analysis is highly sensitive and specific but carries the potential for false-positive results. Cultures are recommended only with epidemiologic studies.

Serious complications of *C. difficile* colitis include toxic megacolon and colonic perforation, which may necessitate a total colectomy. Renal failure, shock, and death have occurred with increasing frequency since the recognition of the new virulent *C. difficile* strain NAP-1/027. This strain is also responsible for a rise in the infection recurrence rate since 2001 (Johnson 2009).

Treatment of *C. difficile* infection includes discontinuation of all antibiotics implicated to play a role in the genesis of the infection. This strategy can resolve acute symptoms, but a significant number of patients need additional treatment. Historically, metronidazole and vancomycin have been used as first-line treatment of mild to moderate *C. difficile* infections at the expense of high recurrence rates and unwanted changes in the intestinal flora. Metronidazole has high systemic absorption; therefore, side effects such as nausea, headache, taste alteration, and peripheral neuropathy are not uncommon (Louie et al. 2011). When usingvancomycin, it is given orally at 125 mg 4 times a day for 10 or 14 days. In patients with ileus, 500 mg of vancomycin is delivered to the right colon via enema every 6 h.

Despite adequate treatment, 20–30 % of patients with *C. difficile* infections experience recurrence. This may be caused by reinfection with a different strain or persistence of infection with the same strain. A first recurrence is treated similarly to the first episode, but for patients with more than one recurrence or severe disease, the use of fidaxomicin, a macrolide antibiotic recently approved for the treatment of recurrent *C. difficile* infection, is indicated (Louie et al. 2011). Unlike vancomycin, fidaxomicin is bactericidal, and it has a prolonged postantibiotic effect, spares *Bacteroides* organisms in the fecal flora, and has resulted in markedly reduced recurrence rates. Unfortunately, this favorable clinical profile does not pertain to infections with the virulent NAP-1 strain.

Probiotics (e.g., *Saccharomyces boulardii*) may be helpful in combination with vancomycin in treating *C. difficile* infections. Patients with recurrent or severe refractory infections generally have poor immune response to toxins A and B. IV immune globulin G and immunization may have therapeutic roles, as well. Rifaximin, a minimally absorbed antibiotic, is recommended as a "chaser," but the epidemic strain B1/NAP-1/027 is increasingly resistant to it. Fecal transplantation, in which donor stool is instilled via a nasogastric tube, seems to be an intriguing therapeutic modality, as it may be effective in reconstituting the gut flora (Johnson 2009).

A newer agent under investigation, the antibacterial lipopeptide CB-315, promises similar advantages but, again, does not seem to be more effective against the NAP-1 strain than other agents (Cubist Pharmaceuticals 2012).

Chemotherapy- and Radiation-Related Diarrhea

Chemotherapy, by virtue of its cytotoxicity in tissues with high metabolic activity such as the small bowel and colon epithelium, causes mucosal damage and alters absorption capability. Chemotherapy-related diarrhea is usually self-limited but is exacerbated by oral intake and may be severe enough to warrant hospitalization. The main therapeutic necessity is to maintain an adequate fluid and electrolyte balance. Some of the more problematic chemotherapeutic agents regarding diarrhea incidence include 5-fluorouracil (5-FU), methotrexate, irinotecan, and cisplatin. Capecitabine is metabolized to 5-FU, and diarrhea is a dose-limiting side effect of it (Davila and Bresalier 2008).

When given with leucovorin, a 5-FU bolus may cause severe symptoms, more so than when given as a continuous infusion. Moreover, risk factors increase susceptibility to diarrhea in patients who receive this treatment. These include female sex, presence of an unresected tumor, previous diarrhea induced by chemotherapy, and use of 5-FU during summer (Davila and Bresalier 2008).

Irinotecan may cause both early—within a few hours after infusion—and late diarrhea. Early diarrhea is mediated by a cholinergic mechanism and is often associated with cramping, salivation, and lacrimation. These symptoms are controlled with the use of loperamide and atropine. The mechanism of irinotecan-induced late diarrhea is poorly understood, as it may happen at any time after infusion and is completely unpredictable but may be mitigated if irinotecan is given every 3 weeks. Combined administration of irinotecan, 5-FU, and leucovorin is particularly troublesome, as is the addition of a 5-FU bolus and leucovin to treatment with oxaliplatin (Davila and Bresalier 2008).

Radiation therapy-induced diarrhea is secondary to mucosal injury and may be worsened by the addition of chemotherapy, especially with 5-FU. Acute diarrhea develops after 1–2 weeks of treatment. Small-bowel involvement causes profuse diarrhea. If prolonged, it may lead to malabsorption and weight loss. Acute radiation proctitis occurs within 6 weeks of therapy and resolves in 6 months. Symptoms include urgency, tenesmus, and bleeding. Chronic diarrhea appears a year or more after exposure to radiation and is characterized by mucosal atrophy and fibrosis. Treatment may require argon plasma coagulation for bleeding. Up to a third of patients with chronic radiation enteritis need surgery for strictures, fistulas, and perforations with significant complications and mortality (Theis et al. 2010).

In the absence of infection, treatment of both chemotherapy- and radiation therapy-related diarrhea should focus on avoiding dehydration, correction of electrolyte imbalances, and, if necessary, aggressive use of antidiarrheal medications such as opioid agonists. Loperamide (Imodium) given initially at 4 mg followed by 2 mg every 4 h until the diarrhea subsides and 2 diphenoxylate (Lomotil) tablets taken every 6 h are commonly used. Octreotide, a long-acting synthetic somatostatin (SST) analog, may be used for more refractory cases, and tinctures of opium, paregoric, codeine kaolin, and charcoal are helpful (Eng 2009).

GVHD

The most common cause of diarrhea in hematopoietic transplant recipients, especially allogeneic bone marrow transplant recipients, is GVHD. Acute GVHD was traditionally thought to occur within 100 days after hematopoietic stem cell transplantation, with chronic GVHD developing thereafter. The recent emphasis has been on the histologic pattern of GVHD. Acute GVHD exhibits essentially the features of acute inflammation and of donor lymphocytes attacking recipient antigens, whereas chronic GVHD features the later fibrosing consequences. Biopsy analysis of the stomach, small bowel, and rectal mucosa in patients with acute GVHD

characteristically demonstrates apoptosis, and vacuolar degeneration may be present in the skin (Washington and Jagasia 2009).

Acute GVHD attacks the GI tract, causing secretory diarrhea with watery stool that may be bloody. Nausea, vomiting, cramping, weight loss, and dysphagia are also associated symptoms (Akpek et al. 2003). Other manifestations include maculopapular/papular skin rash and hepatitis. GVHD may be mild to severe depending on the degree of human leukocyte antigen disparity. These very fragile patients are subject to intensive pretransplant preparation, and the full range of diagnostic possibilities must be entertained. More than one problem may be present.

In patients with chronic GVHD, the esophagus is frequently involved. Fibrosis may cause webs, strictures, and dysphagia. Obstructive lung disease, cholestasis, and scleroderma-like skin findings are observed. Biopsy analysis of skin or components of the GI tract is helpful. An acute GVHD episode may flare and confuse the picture, and infection is still the most common cause of death (Akpek et al. 2003). Treatment of acute GVHD consists of the use of steroids. Methylprednisolone (2 mg/kg/day) is effective in the majority of cases, but mortality rates remain high (Kurbegov and Giralt 2006).

Secretory Diarrhea

Secretory diarrhea is caused by abnormal ion transport and subsequent water secretion. Patients with neuroendocrine tumors deserve special consideration.

Neuroendocrine Tumors and Diarrhea

The cells of the neuroendocrine system are located throughout the body. Formerly known as enterochromaffin cells, they must be located close to their target tissues, as their active secretions are rapidly metabolized. Even the most common neuroendocrine tumor type, carcinoid, is unusual, and VIPomas are exceedingly rare. These tumors secrete a variety of active substances that account for the various syndromes seen in patients with these lesions.

Carcinoids are the earliest described and easily most common neuroendocrine tumors. They may be components of multiple endocrine neoplasia type 1. Carcinoids secrete serotonin, motilin, and substance P, with subsequent increased motility in the small and large intestines. Ten percent of carcinoid patients exhibit the syndrome requiring liver or bone metastases or a pulmonary tumor origin. This allows for active substances to escape liver metabolism as they bypass the portal circulation (Yeung and Gagel 2009). Increased serotonin levels are detected using 24-hour 5-hydroxyindoleacetic acid measurement, and lesions are localized using imaging studies, including indium pentetreotide scintigraphy. Localized disease is treated surgically. Debulking and use of I-131 SST analogs as targeted therapy may provide symptomatic relief. These analogs control symptoms as described below

(Yeung and Gagel 2009). VIPoma syndrome includes watery diarrhea, hypokalemia, and achlorhydria. Patients with this syndrome have elevated serum vasoactive intestinal peptide levels. The majority of peptides are found in the pancreas, with the rest found in the duodenum and retroperitoneum. A carcinoid is a slow-growing tumor, and many carcinoids are treated with surgery. Even hepatic metastases of carcinoids may be resectable or amenable to embolization. Treatment with SST analogs provides relief in nonresectable cases (Yeung and Gagel 2009).

Standard chemotherapy is both ineffective against carcinoids and associated with severe toxic effects. On the other hand, SST analogs provide symptomatic relief and may inhibit the growth of these tumors. SST inhibits all known GI hormones via binding to a class of membrane receptors. Tumors arising in SST target tissue express these receptors unless they are poorly differentiated. However, SST is quickly metabolized and not useful clinically. Octreotide and lantreotide are analogs that combine antitumor activity with metabolic stability. Long-acting versions of these agents that are self-administered have sustained activity levels with mild side effects. They are useful in treating acromegaly, pancreatic islet cell tumors, and GI neuroendocrine tumors. These agents also prevent or improve flushing and diarrhea in patients with carcinoid syndrome. Furthermore, they are equally effective against vasoactive intestinal peptide diarrhea (Modlin et al. 2010).

Octreotide LAR injected at 30–60 mg every 4 weeks has replaced daily dosing of this agent. Lantreotide Autogel administered at 60, 90, or 120 mg monthly via deep subcutaneous injection is equally effective. Pasireotide is a newer agent that may be beneficial in patients with tumors resistant to the other agents (Modlin et al. 2010).

Neutropenic Enterocolitis (Typhlitis)

Typhlitis is characterized by right lower quadrant pain and fever in patients with neutropenia following administration of cytotoxic agents. It occurs most frequently in patients with hematologic malignancies: acute leukemia, myelodysplastic syndrome, or multiple myeloma. It is also encountered in patients with any type of immunodeficiency, such as acquired immunodeficiency syndrome, and with granulocytopenia of any origin.

Neutropenic enterocolitis results from a number of factors that coalesce to induce disease. Mucosal injury caused by cytotoxic drugs in association with an abnormal host response and infiltration of the intestinal mucosa by leukemic cells favor bacterial invasion and the production of endotoxins and necrosis. The cecum is almost always involved; the terminal ileum also may be affected. The cecum is highly distensible and has a relatively poor blood supply. Pathologic findings have revealed edema and inflammation of the intestinal wall, hemorrhages, and necrosis. Physicians have isolated several bacteria from peritoneal fluid and surgical specimens obtained from patients with neutropenic enterocolitis, most frequently *Clostridium septicum* and gram-negative rods (Davila and Bresalier 2008).

Clinical Manifestations

The clinical manifestations of neutropenic enterocolitis include right lower quadrant pain, fever, abdominal distention, and bloody diarrhea in neutropenic patients. In very severe cases, signs of bowel perforation and shock may be present. Diagnosis is based on clinical suspicion and radiologic findings. A CT or magnetic resonance imaging scan will show edema, wall thickening, a fluid-filled dilated cecum, and localized pneumatosis or free air.

Treatment

Conservative measures are recommended for treatment of neutropenic enterocolitis, such as bowel rest, nasogastric suction in cases of ileus, parenteral nutrition, and use of wide-spectrum antibiotics. Correction of neutropenia with administration of granulocyte colony-stimulating factor accelerates recovery. Surgery is indicated for patients with intractable bleeding or bowel perforations (Davila and Bresalier 2008).

Esophagitis

In cancer patients, esophagitis may be caused by the cancer or its treatment. Odynophagia and dysphagia result from damage caused by a primary tumor or metastatic spread. Also, the fixed esophagus is vulnerable to insult from radiation therapy for lung or breast cancer. Chemotherapeutic agents such as doxorubicin, bleomycin, cyclophosphamide, and cisplatin may worsen the injury. Finally, the immunocompromised state of a treated patient may allow for viruses, fungi, and bacteria to cause opportunistic infections.

Candida albicans is the most common fungus identified in patients with esophagitis. The infection may be accompanied by oral thrush. Use of histamine type 2 blockers or proton pump inhibitors is a predisposing factor for esophagitis. Endoscopy reveals white mucosal lesions with erythematous haloes. Fluconazole administered at 100–200 mg for 14–21 days is the treatment of choice. It is administered intravenously to immunocompromised patients (Davila and Bresalier 2008).

Herpes simplex virus, cytomegalovirus, and varicella zoster virus are the viruses most often encountered in patients with esophagitis. It is diagnosed using endoscopy with brushings and biopsy. In patients with herpes simplex virus infections, cytology reveals intranuclear inclusions, and culture may be positive for infection. This infection is treated with 400 mg of acyclovir given orally 5 times a day for 14–21 days or 5 mg/kg acyclovir given intravenously every 8 h for 7–14 days. Cytomegalovirus infection is found only in immunocompromised hosts. Endothelial cells and fibroblasts are infected in these patients, causing deep ulceration. Gancyclovir given at 5 mg/kg twice daily and foscarnet given at 90 mg/kg twice daily are the agents of choice for this infection. Varicella zoster virus infection

occurs in the setting of disseminated disease and is treated with IV acyclovir. Polymicrobial bacterial infections are found in patients with neutropenia and treated with broad-spectrum antibiotics (Davila and Bresalier 2008).

In addition to treatment directed at the infecting organism, supportive measures are necessary for esophagitis. Dietary modifications such as use of cool liquids may make oral intake tolerable. Taking viscous lidocaine before meals may help with this. In patients with severe symptoms, IV administration of medication may be necessary. Radiation esophagitis that progresses to stricture formation is managed with dilation or stenting.

Malignant Gastroparesis

Gastroparesis is delayed gastric emptying in a nonobstructed stomach. In cancer patients, it is caused primarily by GI tract malignancies, genitourinary cancers, and carcinomas of unknown primary. Other gastroparesis factors include prior pancreaticoduodenectomy for pancreatic cancer (Whipple procedure), gastrectomy, and liver surgery. Postgastric or duodenal obstructions followed by stent placement are other causes of gastroparesis. Anti-Hu antibodies are specific markers for a paraneoplastic presentation of small-cell lung cancer in patients presenting with severe gastroparesis (Revicki et al. 2004). Noncancerous etiologies related to gastroparesis are diabetes mellitus and idiopathic gastroparesis.

Symptoms of delayed gastric emptying include persistent nausea, vomiting, bloating, early fullness, inability to complete meals, and subjective abdominal discomfort. The Gastroparesis Cardinal Symptom Index is a validated tool for assessment of symptoms of gastroparesis (Olausson et al. 2008). Diagnostic tests for gastroparesis include the gastric scintigraphy-liquid phase gastric emptying study, 13C-octanoic acid breath test, and acetaminophen absorption test.

Treatment of gastroparesis is aimed at correction of symptoms, fluid/electrolyte management, and nutritional support. Pharmacologic management includes prokinetics such as metoclopramide and oral erythromycin. Metoclopramide is useful but associated with neurologic side effects, with altered mental status and tardive dyskinesia, and has a black box warning for prolonged or high-dose use. Domperidone is available in the United States by filing an investigational new drug application to the U.S. Food and Drug Administration after local institutional review board approval. Erythromycin is effective when given intravenously, but tachyphylaxis develops with oral administration. GI side effects that mimic symptoms of gastroparesis limit the use of erythromycin.

Management of nutrition includes eating small meals at frequent intervals, consuming supplemental nutritional drinks focused on low osmolality, and maintaining a low-fat and -fiber diet. Staying upright and favoring the right lateral lying position after a meal are also advocated (Olausson et al. 2008). A venting gastrostomy can provide relief of symptoms. Feeding gastrostomy or jejunostomy is the mainstay of nutritional support. Researchers have studied the use of gastric pacemakers in diabetic gastroparesis patients but not in cancer patients.

MBO

MBO is defined as "clinical evidence of bowel obstruction (history/physical/radiological examination); bowel obstruction beyond the ligament of Treitz, in the setting of a diagnosis of intra-abdominal cancer with incurable disease, OR a diagnosis of non-intra-abdominal primary cancer with clear intraperitoneal disease" (Ripamonti et al. 2008). The most common malignancies causing bowel obstruction are cancers of the ovary, colon, and stomach. About 10–28 % of patients with GI malignancies experience MBO, whereas 20–50 % of patients with ovarian carcinoma have bowel obstruction (Feuer and Shepherd 2002). Extra-abdominal malignancies that cause bowel obstruction include breast cancer, melanoma, and lung cancer, which do so by virtue of intraperitoneal spread.

Clinical Diagnosis of MBO

Classically, patients with MBO have a history of waxing and waning bowel habits followed by intermittent self-resolved obstructions. The symptoms of MBO include colicky abdominal pain, decreased frequency of bowel movements, and change in size and character of stool, which are managed at times by the patients themselves with bowel rest and resolution of symptoms by having a few bowel movements. Late-stage obstructions are characterized by unresolved severe abdominal pain, distension, nausea, and vomiting of fluid ranging from bilious to coffee-ground to foul-smelling and feculent. Peritoneal signs, sepsis, and shock may be observed in severe cases.

Causes of Bowel Obstruction in Cancer Patients

Mechanical

- Peritoneal carcinomatosis
- Primary tumor obstruction at presentation
- Recurrent tumor at anastomosis after surgery
- Adhesions/scars after surgery for cancer or other previous surgeries
- Postirradiation fibrosis
- Intra-abdominal abscess with mechanical compression
- Metastasis with a mass in the mesentery or omentum
- Lesions from pelvic tumors with drop metastasis or primary ovarian cancer
- Linitis plastica of the stomach

Functional (Ileus)

- Use of opiates for pain
- Peritoneal carcinomatosis and myenteric plexus involvement causing malignant dysmotility
- Ogilvie syndrome (colonic pseudo-obstruction)
- Paraneoplastic syndromes with neuronal involvement

Evaluation

Initial evaluation of MBO always includes a 4-view abdominal X-ray when obstruction is suspected in the physician's clinical assessment. A subsequent CT scan can be done, which, according to protocol, includes oral, IV, and rectal contrast administration unless contraindicated. The benefits of CT include finding the level of obstruction and predicting the type and operability of the obstruction, tumor burden, and ascites. Additional testing may consist of an upper GI (UGI) series with appropriate contrast material (water-soluble hypertonic contrast or nonionic, low-osmolar contrast medium), which helps identify multilevel obstructions and define the functional movement of the bowel. In rare instances, magnetic resonance imaging may help define soft tissue masses in conjunction with an obstruction.

Management of Bowel Obstruction

Patients with MBO have several treatment options. Careful evaluation of the patient according to severity and level of obstruction, disease stage, performance status, prognosis, and future cancer treatment will determine the treatment modality.

Initial treatment consists of nasogastric tube decompression with pain and nausea control along with IV fluids. If the obstruction is acute, emergent surgery may be indicated. Patients with MBO owing to peritoneal carcinomatosis have very poor responses to surgery, with high morbidity and mortality rates (Abbas and Merrie 2007; Helyer et al. 2007). These patients benefit from a more conservative approach aimed at decreasing bowel contractions and fluid secretion and accumulation with subsequent improvement in nausea, vomiting, and abdominal pain. The use of anticholinergic agents (e.g., hyoscine butylbromide), antispasmodics, corticosteroids, and the SST analog octreotide has significantly improved symptoms (De Conno et al. 1991; Mystakidou et al. 2002). Parenteral nutrition must be considered early in the course of MBO. If conservative treatment is not successful, other modalities of treatment can be considered, including surgery and endoscopic management.

Surgical Management

Available surgical procedures for MBO include diverting colostomy, intestinal bypass, and adhesiolysis and/or resection in select cases. Patient selection is based on age, nutritional status, performance status, comorbidities, and future treatment plans. Disease-related factors such as operative complications also determine patient eligibility for surgery.

Endoscopic Interventions

Venting gastrostomy for any level of obstruction, provided it can be performed safely without ascites complicating the track, is a palliative procedure performed often in patients with MBO. Colorectal obstructions are frequently amenable to

stenting. Stents generally provide colonic decompression, with resolution of symptoms in more than 75 % of patients (Law et al. 2000; Mainar et al. 1999). Potential complications of stenting are perforation, stent migration, and reobstruction. Rectal bleeding, anorectal pain, and tenesmus are also possible.

In summary, management of bowel obstruction requires a multimodality approach, including prompt surgical evaluation to prevent more serious complications.

GI Bleeding in Cancer Patients

GI bleeding is a common emergency in cancer patients that can lead to significant morbidity and death depending on the amount of blood lost, the patient's medical comorbidities, and how quickly care is administered.

Initial management of GI bleeding is similar in patients with and without cancer. However, special consideration must be given to patients with cancer to address their complicating factors, including hematologic, metabolic, and structural abnormalities resulting from their malignancies and treatments. Therapeutic interventions for GI bleeding require a multidisciplinary approach, including input from emergency room physicians, hospitalists, gastroenterologists, interventional radiologists, and surgeons.

Etiology and Clinical Manifestations

The clinical manifestations of GI bleeding depend on the site. UGI bleeding originates above the ligament of Treitz and appears as hematemesis or melena or as occult fecal blood detected via chemical testing. When the bleeding is brisk, it may manifest as hematochezia.

Lower GI bleeding originates below the ligament of Treitz and presents as hematochezia, usually indicating a left-side colon and rectum pathology, or as occult blood when the source is the small bowel or right colon.

In addition to the common causes of GI bleeding seen in patients without cancer, specific conditions may cause bleeding and exacerbate this problem in those with cancer. These include thrombocytopenia, radiation therapy, chemotherapy, and tumor erosion.

Common Causes of UGI Bleeding

Conditions usually diagnosed using upper endoscopy:

- Esophagitis/esophageal erosions
- Mallory-Weiss tears
- Esophageal/gastric/duodenal tumors (benign and malignant)

- Esophageal/gastric varices
- Peptic ulcers
- Portal hypertensive gastropathy
- Duodenitis/gastritis/erosions
- Arteriovenous malformations
- Aortoduodenal fistulae
- Dieulafoy lesions (abnormally large tortuous submucosal artery)

Common Causes of Lower GI Bleeding

Conditions usually diagnosed using colonoscopy:

- Hemorrhoids
- Diverticular disease
- Inflammatory bowel disease
- Angiodysplasia
- Benign and malignant neoplasms
- Ischemic colitis
- Radiation colitis
- Colonic ulceration
- Postpolypectomy bleeding
- Anal fissures

Upper and lower endoscopy may fail to find the cause of bleeding when it originates in the small bowel. Causes of this obscure GI bleeding include:

- Small bowel ectasia
- Small bowel adenocarcinoma
- Small bowel stromal tumors
- Meckel diverticulum
- Ectopic varices
- Hemobilia
- Aortoenteric fistulae

Cancer Patients: Special Situations

A wide variety of cancers may metastasize to the stomach, proximal duodenum, or regional lymph nodes and then erode into the GI lumen, leading to blood loss. Certain tumors have a propensity for erosion and hemorrhage, especially gastric mucosa-associated lymphoid tissue lymphomas, which are implicated as important causes of UGI bleeding.

Mucositis caused by chemotherapy may lead to clinically significant GI bleeding. Nausea and vomiting resulting from chemotherapy are common and may provoke hematemesis from Mallory-Weiss tears. Also, patients taking adjuvant nonsteroidal anti-inflammatory drugs to control cancer-related pain have an increased risk of bleeding from peptic ulcers.

Patients undergoing radiation therapy for thoracic neoplasms are at risk for radiation-induced mucosal injury resulting in bleeding. Radiation effects and direct tumor extension can cause fistula development to the aorta and other vascular structures and massive UGI bleeding.

Portal hypertension can develop from tumor infiltration of the liver, leading to variceal bleeding. In addition, intensive care unit-related stress ulcers are common complications in cancer patients.

Neutropenic enterocolitis results from a combination of GI mucosal injury caused by use of cytotoxic drugs, profound neutropenia, and impaired host defenses, allowing for polymicrobial bacterial and fungal invasion. It can lead to necrosis of the bowel wall and mostly involves the cecum, right colon, and ileum, causing bloody diarrhea (Davila and Bresalier 2008).

In severe cases, GVHD in the GI tract can cause significant bleeding requiring transfusion of several units of blood a day.

Infectious diarrhea caused by community-acquired pathogens (*E. coli* 0157 and *Salmonella*, *Shigella*, and *Campylobacter* spp.) or opportunistic organisms such as cytomegalovirus is common in cancer patients. It may be associated with occasional significant lower GI bleeding.

Radiation proctitis occurs within 6 weeks after acute external radiation therapy and causes bleeding from friable mucosal telangiectasias. A delayed chronic form can occur 9–15 months after radiation therapy, with bloody diarrhea and tenesmus. Also, lower GI bleeding can develop in patients who undergo prostatic brachytherapy 4–16 months after implant placement (Davila and Bresalier 2008).

Administration of bevacizumab, a monoclonal antibody against vascular endothelial growth factor used in the treatment of various cancers, has been associated with GI perforation, fistula formation, and bleeding (Davila and Bresalier 2008).

Diagnostic Evaluation and Treatment

Cancer patients presenting with UGI bleeding should undergo timely evaluation. The timing of their interventions depends on the stability of their vital signs and quantity of bleeding as assessed in the initial history. Proximal causes and contributing factors are identified. Initial stabilization includes rapid assessment of the patient's airway, breathing, circulation, IV access, and initial blood work. Other interventions that may be appropriate include nasogastric lavage to confirm the source and briskness of bleeding. However, a nonbloody aspirate does not exclude

recent gastric or duodenal bleeding, as bleeding may have occurred earlier and may be distal to the ligament of Treitz.

Initial measures in patients with GI bleeding include insertion of large-bore IV access, volume resuscitation with crystalloids in addition to blood components, oxygenation, and monitoring. Transfusion of fresh frozen plasma and/or platelets may be necessary in patients with coagulopathy or thrombocytopenia, as these conditions tend to be common in cancer patients.

Initial empiric treatment with a proton pump inhibitor is recommended before endoscopy. This treatment is postulated to promote hemostasis by neutralizing pH even in cases of bleeding not related to acid exposure. Treatment with a proton pump inhibitor (omeprazole or pantoprazole) is started intravenously with a bolus of 80 mg followed by a drip rate of 80 mg/h. Physicians have used esophagogastroduodenoscopy to evaluate patients before and after treatment with a proton pump inhibitor and demonstrated improvement in erosive and ulcerative lesions. IV infusion of erythromycin in a 250-mg bolus or at 3 μg/kg over 30 min can be given 30–90 min before esophagogastroduodenoscopy to facilitate gastric emptying of retained foods.

Therapy with SST or an analog of it may be initiated if variceal bleeding is suspected and continued for 3–5 days, as it reduces portal pressure. Injection sclerotherapy and ligationare the preferred treatment modalities for control of variceal bleeding. Patients with uncontrolled or recurrent bleeding must be considered for transjugular intrahepatic portosystemic shunting or transarterial chemoembolization (Garcia-Tsao and Bosch 2010).

Locating the approximate site of bleeding according to stool characteristics is usually imprecise, as it depends on the briskness of the bleeding and rate of passage of stool through the GI tract.

Initial evaluation of GI bleeding assesses the stability of the patient's cardiovascular system, which is achieved with good large-bore vascular access plus blood work with typing and cross-matching for transfusion, if needed. Colonoscopy usually localizes and diagnoses the cause of bleeding expeditiously. Biopsy specimens can be taken, and non-cancer-related bleeding can be excluded.

Radionuclide imaging is considered when colonoscopy is negative for bleeding or the source of bleeding is suspected to be the small bowel. This imaging modality is more sensitive than angiography, as it requires a lower bleeding rate, but it is less specific than angiography. Capsule endoscopy is superior to other modalities in evaluating the small bowel, especially in cases of obscure GI bleeding.

CT angiography with multidetector helical scans requires active bleeding for good localization. Mesenteric angiography requires ongoing blood loss of 1.0–1.5 mL a minute for the bleeding to be well visualized. It also affords therapeutic options to control bleeding that other modalities do not, including vasoconstriction with vasopressin and micro-embolization with a variety of substances. Consideration of mesenteric angiography may be useful for patients who are not candidates for surgery (Davila et al. 2005).

Ascites

Ascites is a frequent complication in cancer patients, particularly those with malignancies of the breast, stomach, colon, or pancreas. It is also encountered in patients with ovarian or appendiceal disease owing to local extension. The pathophysiology of ascites differs according to the type of tumor, and it may be benign or malignant. Nonmalignant ascites owing to cirrhosis or portal hypertension is also common.

Malignant ascites may be caused by peritoneal carcinomatosis. Cancer cells on the peritoneal surface produce a proteinaceous exudate that accumulates in the abdominal cavity. Ascites also may result from an increase in portal pressure caused by massive liver metastases, direct tumor invasion or compression of the porta hepatis or mesenteric and splenic vessels, or thrombosis of the portal vein.

Ascites is associated with portal hypertension, which leads to splanchnic vasodilatation owing to increased production of local vasodilators. These two factors increase intestinal capillary pressure and permeability with the subsequent accumulation of peritoneal fluid. As the disease progresses, the magnitude of vasodilatation is such that the arterial circulating volume decreases markedly. To maintain adequate cardiac output, compensatory mechanisms that result in water and sodium retention and volume expansion are activated (Gines et al. 2004).

Chylous ascites is a much less common etiology caused by lymphatic obstruction, which can occur in patients with lymphoma.

Clinical Manifestations

Abdominal distention and weight gain are the usual physical manifestations of ascites. Examination will reveal increased girth and dullness to percussion. Clinical diagnosis of ascites is often confirmed via ultrasound, which can detect as little as 100 mL of excess fluid. A sympathetic pleural effusion may be present in up to 10 % of cases, more often on the right than the left. Pain should raise the suspicion of an infection, especially in the presence of fever.

Evaluation

All patients with new findings of ascites undergo diagnostic paracentesis. Routine tests of the ascitic fluid include albumin analysis, a cell count with differential, cultures, and sensitivity and cytologic analysis for cancer patients. For patients who undergo culture, blood culture bottles are inoculated at the bedside. A Gram stain usually is not helpful. Other tests to be considered are triglyceride measurement for patients with chylous ascites, acid-fast staining, tuberculosis culture, and glucose,

amylase, and bilirubin measurement in the appropriate clinical settings. The serum albumin level is measured at the same time to establish the serum-ascites albumin gradient, which correlates directly with the portal pressure. The gradient is calculated by subtracting the albumin level in the ascitic fluid from the serum albumin level. A serum-ascites albumin gradient greater than 1.1 g/dL indicates portal hypertension.

Treatment

Benign ascites caused by portal hypertension is treated conventionally. This includes sodium restriction and use of diuretics. A diet containing 1.5–2.0 g of sodium per day with administration of a combination of spironolactone and furosemide once daily is recommended as the initial therapy. The diuretic dosages are escalated to maintain a spironolactone:furosemide ratio of 100:40 for potassium balance. Caution is required, as significant diuresis may worsen hyponatremia and precipitate renal failure and encephalopathy. Ascites becomes refractory to treatment once doses of 400 mg of spironolactone and 160 mg of furosemide are reached without successful control of the ascites. Repeated moderate- to large-volume paracentesis (more than 5 L) using plasma expanders to prevent hemodynamic instability is required for relief of ascites.

Physicians have used transjugular intrahepatic portosystemic shunts in the management of refractory ascites with some efficacy. The main problems with this procedure are stent stenosis with recurrence of ascites and increased incidence of hepatic encephalopathy. Peritoneovenous shunting is no longer recommended (Gines et al. 2004).

Treatment of the underlying disease process is required in patients with malignant ascites and carcinomatosis. The prognosis is poor for these patients with the exception of those with ovarian or appendiceal carcinoma, which may respond to extensive debulking and intraperitoneal chemotherapy. Peritoneal carcinomatosis in patients with pancreatic, gastric, colon, breast, or lung cancer carries a dismal prognosis; the aim in these settings is to provide symptom control by means of frequent paracentesis or placement of an intraperitoneal catheter. Drawing off fluid in managed settings may be surprisingly well tolerated. In cases of large-volume ascites, large-volume paracentesis is fast, effective, and better tolerated than are high-dose diuretics. Plasma expanders diminish circulatory dysfunction and the risk of precipitating hepatorenal syndrome. Treatment with albumin is superior to that with other agents and is recommended (Gines et al. 2004).

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis almost always occurs in the setting of ascites. It is usually caused by hepatic cirrhosis but can be secondary to metastatic disease. Ascitic fluid provides a favorable growth medium for bacteria, and it is presumed to be seeded in the course of transient or ongoing bacteremia. Clinical manifestations of bacterial peritonitis are fever, abdominal pain, and altered mental status, although

some patients present with mild abdominal tenderness only, and fever may be absent. An absolute neutrophil count in the ascitic fluid greater than 250 cells/mm or a bacterium-positive culture is diagnostic of bacterial peritonitis. Enterobacteriaceae species, *Streptococcus pneumoniae*, and enterococci are the most frequently isolated pathogens. The presence of multiple organisms or anaerobes suggests secondary peritonitis as seen in patients with peritoneal perforation.

Diagnosis of spontaneous bacterial peritonitis requires a high index of suspicion, and the absence of fever or even a bacterium-negative culture does not rule out an infection. Ten milliliters of fluid should be injected into the blood culture bottle at the bedside. Blood culture will often reveal concomitant bacteremia. If clinical suspicion of bacterial peritonitis persists despite negative test results, a repeat paracentesis is indicated.

Secondary peritonitis should always be considered, requiring the use of CT with contrast as well as a plain X-ray for detection of free air.

Pending the results of blood and peritoneal fluid culture and sensitivity testing, empiric therapy for infection with Gram-negative aerobic bacilli and Gram-positive cocci, such as a third-generation cephalosporin, is initiated. When sensitivities are known, more focused therapy is initiated. Treatment for up to 2 weeks may be needed depending on the response. If the patient does not exhibit clinical improvement, diagnostic paracentesis is repeated. After the initial treatment, long-term antibiotic-based prophylaxis is indicated, as the recurrence rate for spontaneous bacterial peritonitis is about 70 % at 1 year. Current recommendations favor the use of high-dose fluoroquinolones once a week (Gines et al. 2004).

Hepatorenal syndrome is a severe complication of spontaneous bacterial peritonitis and has a very high mortality rate. Some studies have demonstrated that the use of IV albumin at 1.5 g/kg on day 1 and 1.0 g/kg on day 3 after diagnosis decreases the incidence of hepatorenal syndrome and probably increases survival durations (Gines et al. 2004).

Hepatic Encephalopathy

Hepatic encephalopathy is a potentially reversible complication of liver cirrhosis. The manifestations of it are neuropsychiatric and consist of a variety of symptoms. These symptoms range from coma with severe hepatic encephalopathy to very subtle cognitive deficits, with a wide array of symptoms in between, such as impaired memory, psychomotor disturbances, and disorientation. Hepatic encephalopathy may be acute, recurrent, or chronic.

Pathophysiology

The pathophysiology of hepatic encephalopathy is complex and not completely understood. It is believed to be secondary to systemic accumulation of neurotoxins from the intestinal tract owing to impaired liver metabolism. This results from

hepatocellular dysfunction, portosystemic shunting, or a combination of the two. These neurotoxins are mainly ammonia and deaminated glutamine, whose production is increased by urease-positive intestinal flora, although a variety of metabolites are thought to be involved. Failure to detoxify the products of digestion causes buildup in the systemic circulation and diffusion into the central nervous system. A precipitating event, such as sepsis, GI bleeding, spontaneous bacterial peritonitis, dehydration, overly aggressive diuresis, electrolyte imbalance, renal failure, and transjugular intrahepatic portosystemic shunt placement, is frequently identified. Intestinal bleeding is commonly implicated, as it leads to an increased protein burden in the GI tract.

Clinical Manifestations

An increased index of suspicion of hepatic encephalopathy is warranted in the setting of hepatocellular impairment and portosystemic shunting. Altered mental status may vary from mild confusion to deep coma. Neuromotor dysfunction manifests with a variety of features, such as rigidity, asterixis, hyperreflexia, and myoclonus. Characteristically, correction of the underlying precipitant of hepatic encephalopathy leads to symptom reversal. The differential diagnosis is extensive and includes but is not limited to alcohol intoxication, sedative overdose, meningitis, hypoglycemia, Wernicke encephalopathy, and Korsakoff psychosis. These and other possibilities must be considered and ruled out using the usual modalities. Indeed, comorbidities are common.

Treatment

The treatment of hepatic encephalopathy is derived from the hypothesis of systemic ammonia accumulation favored by the presence of ammonia-forming bacteria in the gut. In addition to identification and treatment of the precipitating event, a nonabsorbable disaccharide such as lactulose is given to increase gut motility and decrease ammonia absorption in patients with hepatic encephalopathy. Antibiotics are administered to reduce the intestinal flora and ammonia production. Lactulose and rifaximin, a minimally absorbed antibiotic, are recommended for treatment of acute episodes of hepatic encephalopathy and prevention of recurrence. Recent studies demonstrated that treatment with lactulose and rifaximin alone reduces the risk of an acute episode of hepatic encephalopathy. Furthermore, treatment with rifaximin has decreased the risk of hospitalization by 50 % below that with treatment with a placebo. Other useful antibiotics are neomycin, vancomycin, paromomycin, and metronidazole. However, when given over an extended period, they may have serious side effects, such as ototoxicity, nephrotoxicity, and peripheral neuropathy. The efficacy of other therapeutic approaches, including the use of probiotic agents, has yet to be elucidated. Heroic measures such as liver transplantation may be considered (Bass et al. 2010).

Acute Pancreatitis

Acute pancreatitis is a well-known entity in cancer patients that is a consequence of direct invasion of the pancreatic duct or a blockage owing to lymph node enlargement or is secondary to chemotherapy via various mechanisms.

Etiology

Mechanical ampullary obstruction, gallstones, biliary sludge, pancreatic or periampullary cancer, duodenal stricture or obstruction, alcohol, hypertriglyceridemia (either de novo or drug-induced), hypercalcemia, drugs, infections, trauma, and vascular disease (post-endoscopic retrograde cholangiopancreatography and idiopathic) are the most common causes of acute pancreatitis in the cancer patient. It results from an initial insult to the acinar cells followed by intracellular activation of trypsinogen, leading to further activation of trypsin and other pancreatic enzymes, such as phospholipase, chymotrypsin, and elastase. Trypsin in turn activates the complement cascade, the kinin-kallikrein system, coagulation, and fibrinolysis. This intrapancreatic release of active enzymes leads to autodigestion, resulting in a vicious cycle of active enzyme-induced damage of cells, which then release more active enzymes. The destruction spreads along the pancreas and into the peripancreatic tissue.

Alcohol- and drug-induced pancreatitis may result from the direct toxic effects of the offending agent. If pancreatic damage is severe, systemic complications, including fever, acute respiratory distress syndrome, pleural effusions, renal failure, shock, and myocardial depression, may develop. This systemic inflammatory response syndrome is mediated by activated pancreatic enzymes (phospholipase, elastase, trypsin, etc.) and cytokines (tumor necrosis factor and platelet-activating factor) released into the circulation from the inflamed pancreas.

The literature on drug-induced pancreatitis consists mostly of case reports and drug trials in which pancreatitis developed during treatment with a specific agent, with no other identifiable causes. Acute pancreatitis resolved or improved upon discontinuation of the specific drug and may have recurred upon reinstitution of the medication. Examples include but are not limited to tyrosine kinase inhibitors used for treatment of leukemias, tamoxifen, capecitabine (via hypertriglyceridemia), carboplatin, docetaxel, sorafenib, and corticosteroids.

Clinical Presentation

Abdominal pain, often with radiation to the back; nausea; vomiting; and agitation are common complaints of patients with acute pancreatitis. The pain is steady and located in the right upper quadrant or epigastrium but can be diffuse or localized to the left upper quadrant. It has a rapid onset, reaching maximum intensity in

10–20 min. A classical presentation of pancreatic pain is its characteristic band-like radiation to the back, with relief while bending forward. Painless pancreatitis can occur in patients on dialysis. Severe pancreatitis attacks may result in shock or coma. Hemorrhagic complications such as retroperitoneal bleeding and bleeding into pseudocysts are uncommon.

Ecchymotic discoloration of the flanks results from retroperitoneal bleeding in patients with pancreatic necrosis. Fever, tachycardia, and, in severe cases, shock and coma may be part of the clinical presentation. Epigastric tenderness is minimal when compared with the patient's discomfort. The patient may have dyspnea and shallow breathing owing to pleural effusion or irritation of the diaphragm. Obstruction of the biliary tract may lead to jaundice.

Diagnosis

In patients with acute pancreatitis, synthesis of pancreatic enzymes by acinar cells continues, with the enzymes spilling out of the cells into the interstitial space and hence the systemic circulation, resulting in elevation of amylase and lipase levels. Elevated serum amylase levels are found with a variety of nonpancreatitic conditions and thus cannot be used alone for diagnosis of acute pancreatitis. Because amylase is cleared through the kidneys, renal failure may result in decreased clearance. Assessment of serum lipase levels is often combined with that of amylase levels to improve diagnostic accuracy. The sensitivity of serum lipase measurement in diagnosing acute pancreatitis ranges from 85 % to 100 %. However, lipase levels can be elevated with a variety of conditions. Levels of pancreatic enzymes such as phospholipase A, trypsin, carboxyl ester lipase, carboxypeptidase A, and colipase are also elevated in serum during acute pancreatitis attacks, but their sensitivity and specificity are not more significant than those of levels of serum amylase and lipase and are not helpful either alone or in combination for diagnosis. In post-endoscopic retrograde cholangiopancreatography pancreatitis cases, measurement of urinary and serum trypsinogen-2 may be helpful in early detection of pancreatitis.

Radiologic Investigations

Imaging plays an important role in diagnosis and management of acute pancreatitis. Abdominal ultrasound helps identify gallstones, biliary dilatation, focal fluid collections, and pseudocysts. Endoscopic ultrasound has a 91 % sensitivity rate in detecting gallbladder calculi, whereas that of transabdominal ultrasound is 50 % (Koo et al. 2010). Endoscopic ultrasound is also used to detect occult tumors and pancreatic duct abnormalities. Abdominal and plain chest radiography helps exclude other causes of acute abdominal pain, such as obstruction and bowel perforation. The radiographic findings for acute pancreatitis range from unremarkable to

localized ileus of a segment of the small intestine (sentinel loop); the colon cutoff sign is seen in more severe cases. Generalized ileus may occur in patients with severe disease. A ground glass appearance may indicate ascites. A chest X-ray may show signs of acute pancreatitis, such as elevation of a hemidiaphragm, pleural effusions, pulmonary infiltrates, and acute respiratory distress syndrome, in one third of patients. Left-sided or bilateral pleural effusions suggest increased risk of complications.

CT is used not only for evaluation but also for classification of acute pancreatitis into low-, medium-, and high-severity groups with correspondingly increased levels of morbidity and mortality.

Magnetic Resonance Cholangiopancreatography

Magnetic resonance cholangiopancreatography plays an important role in patients with elevated creatinine levels who cannot undergo contrast-enhanced CT. It is especially useful for evaluation of the intrahepatic and extrahepatic biliary tree and pancreatic duct. Most recently, the concomitant use of secretin makes magnetic resonance cholangiopancreatography even more helpful in assessing structural etiologies in patients with recurrent acute pancreatitis, as it yields high-quality images of the pancreatic ducts and has high specificity for diagnosing pancreatic duct outflow obstructions when used with manometry and clinical assessment. When biliary obstruction is found to be the cause of pancreatitis, the patient should proceed directly to undergoing endoscopic retrograde cholangiopancreatography. The risk of procedure-related complications must be weighed against the benefit of this procedure.

Complications

Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, complications of it have significant prognostic importance. For example, necrosis, hemorrhage, and infection increase the mortality index. Other complications, such as pseudocyst or pseudoaneurysm formation and venous thrombosis, increase morbidity and mortality to a lesser degree.

Treatment

In most cases, treatment of acute pancreatitis consists of supportive care, with further measures directed at management of complications. Patients having mild gallstone pancreatitis can undergo a cholecystectomy within 48 h after admission. In patients with more severe disease, though, cholesystectomy should be delayed

depending on the clinical scenario. In contrast, a sphincterotomy can be performed as early as possible, especially if the patient has evidence of obstructive jaundice or acute cholangitis.

Acute Cholangitis

Acute suppurative cholangitis is a potentially life-threatening emergency. It is related to obstruction of the common bile duct with various causes, resulting in pus formation and ascending infection into the hepatic ducts and, subsequently, the bloodstream. Common pathogens that cause acute cholangitis include *E. coli* and *Klebsiella*, *Bacteroides*, and *Enterococcus* species.

Malignancy-related causes of acute cholangitis are benign and neoplastic strictures, including cholangiocarcinoma, blockage of the ducts by extrinsic compression by a pancreatic carcinoma, duodenal carcinoma, and porta hepatis nodes from GI malignancies, breast cancer, or lymphoma. An increasingly common cause of cholangitis in cancer patients is postendoscopic or percutaneous drainage of the bile ducts owing to mechanically blocked devices serving as nidi for infection.

Symptoms of acute cholangitis include right upper quadrant pain, fever, and jaundice (Charcot triad). Hypotension and mental status changes suggest increased mortality of cholangitis (Reynolds pentad). Septicemia requires urgent treatment owing to its expected high mortality rate.

Laboratory findings for patients with acute cholangitis may be prominent or subtle and include elevated direct bilirubin, alkaline phosphatase, and, to a lesser extent, transaminase levels. The diagnostic modality of choice is abdominal CT, although right upper quadrant ultrasound may be considered to detect biliary ductal dilatation. An unremarkable sonogram does not negate the diagnosis of acute cholangitis, and clinical suspicion must be confirmed by a CT scan. Broad-spectrum penicillins or a fluoroquinolone with metronidazole is given emergently. IV fluid resuscitation should be aggressive in patients with systemic inflammatory response syndrome owing to infection proceeding to overt septicemia. Additional supportive management includes correction of coagulopathy and electrolyte levels and evaluation of cardiac and pulmonary stability (Takada et al. 2007).

Definitive management of acute cholangitis should be directed toward biliary decompression on an emergent or urgent basis, as it can be life-saving. Endoscopic drainage (endoscopic retrograde cholangiopancreatography) is the preferred method for this. Alternatively, percutaneous drainage can be performed via percutaneous transhepatic cholangiography.

Endoscopic drainage of bile can be done using plastic stents or expandable metal stents. The decision to use either type of stent depends on factors related to planned subsequent treatment of the cancer (curative, presurgical treatment, or palliative chemotherapy) or technical factors (cancerous growth into the bile duct, extrinsic

compression). Plastic stents are easier to place than metal ones, are easily infected, and are changed every 3 months, with the advantage of being removable. Metal stents are permanent and less likely to be infected or obstructed than plastic ones.

Available modalities of percutaneous drainage include an internal or external stent, which aids in biliary drainage internally with one end in the duodenum and externally to an outside drainage bag. The stent can be capped externally once good drainage is established. Isolated external stenting is advocated when internal access is limited (Lee 2009).

Key Practice Points

- The cancer patient presents additional challenges in diagnosis and management owing to the disease itself, comorbidities, and complications related to treatment.
- A high index of suspicion is indicated. Minor symptoms and signs may portend a more serious condition than would be the case in the general population.
- Accurate diagnosis leads to effective treatment.
- Always be aware of the complete clinical context.
- A thorough history and physical examination should not be neglected.
- Appropriate, timely consultations should be performed. This is especially true if a surgical procedure may be indicated.
- GI bleeding may result from or be exacerbated by an underlying bleeding diathesis.
- Serious infections may present with minor findings.
- Symptomatic care is very important. The patient should be made as comfortable as possible.
- Support of family members must not be neglected.

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Chapter 6
Nephro-Urologic Emergencies in Patients with Cancer

Amit Lahoti, Maria Teresa Cruz Carreras, and Abdulla K. Salahudeen

Contents

Chapter Overview

Renal and urologic emergencies are common in patients with cancer and generally require a multidisciplinary approach by the oncologist, emergency room physician, nephrologist, urologist, and interventional radiologist. Acute kidney injury is a

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frequent complication of cancer treatment that has a high mortality rate. Nephrologists are frequently needed to provide supportive dialysis until renal function recovers. More than one half of patients with multiple myeloma present with renal injury, and 10 % of them need dialysis upon initial presentation. Renal function in these patients may rapidly improve with treatment of the myeloma. Patients with cancer may present to the emergency room with severe derangements in electrolyte levels and may need immediate treatment by the emergency room physician to prevent cardiac arrhythmias or renal failure. Hematuria may have a subtle presentation, with only microscopic hematuria noted upon urinalysis examination, whereas patients with severe hematuria may experience hemorrhagic shock. Obstructive uropathy may occur anywhere along the urinary tract and generally requires intervention by a urologist or radiologist to decompress the collecting system.

Introduction

The kidneys receive a larger amount of blood supply per gram from the heart than any other organ. They are important in regulating acid-base balance and electrolyte levels, excreting waste products and fluid, and producing enzymes and hormones. Given their high vascularity, the kidneys are uniquely sensitive to blood-borne toxic drugs, leading to injury and dysfunction. Kidney dysfunction may also occur with distal obstruction of the urinary tract (e.g., ureters, bladder). Furthermore, injury to the kidneys, ureters, or bladder may occur secondary to irradiation or toxins in the urine. This chapter highlights some of the common nephro-urologic issues that are encountered during treatment of cancer.

Acute Kidney Injury in Cancer Patients

Authors have reported that acute kidney injury (AKI) occurs in 4–7 % of hospitalized patients. Depending on both the definition of AKI and cases involved, AKI develops in 13–42 % of critically ill patients with cancer, 8–60 % of whom must undergo renal replacement therapy. Development of AKI has been associated with increased mortality rates, lengths of hospital stay, and health care costs. AKI may also limit further cancer treatment, increase the toxicity or limit the delivery of chemotherapy, and exclude patients with cancer from clinical trials. The etiology of AKI is broadly classified into three main categories: prerenal azotemia, intrinsic renal disease, and postrenal obstruction (Table 6.1).

More than 35 different definitions of AKI are used in the literature, making cross-comparison of study results difficult. Recently, the Acute Dialysis Quality Initiative introduced the risk, injury, failure, loss, and end-stage renal disease (RIFLE) criteria for uniform classification of AKI (Table 6.2). The risk, injury, and failure categories define stages of AKI based on the percent increase in the level of

Table 6.1 Common causes of AKI in patients with cancer

Prerenal azotemia
Volume depletion
Nausea, vomiting, diarrhea
Decreased oral intake owing 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
Allergic interstitial nephritis (penicillins, cephalosporins, fluoroquinolones, NSAIDs)
Crystal nephropathy (methotrexate, acyclovir, ciprofloxacin, sulfonamides, rifampin)
Osmotic nephrosis (IV immunoglobulin, mannitol, starch) Thrombotic microangiopathy (post-HSCT, gemcitabine, prior radiation therapy)
Myeloma-related kidney disease
Postrenal obstruction
Bladder outlet obstruction (malignancy of cervix, prostate, bladder, or uterus)
Retroperitoneal disease (metastasis, lymphadenopathy, fibrosis)
Hemorrhagic cystitis (cyclophosphamide, BK virus)
Ureteral strictures (prior radiation therapy, BK virus)

Table 6.2 RIFLE criteria for AKI

RIFLE stage	Increase in creatinine level	Decrease in urine output
Risk	≥50 % from baseline or 0.3 mg/dL	<0.5 mL/kg/h × 6 h
Injury	≥100 % from baseline	<0.5 mL/kg/h × 12 h
Failure	≥200 % from baseline or need for dialysis	<0.3 mL/kg/h × 24 h or anuria × 12 h
Loss	Persistent AKI >4 weeks	
End-stage renal disease	Loss of renal function >3 months	

serum creatinine relative to the baseline level or presence of oliguria. The loss and end-stage renal disease categories identify patients needing renal replacement therapy for more than 4 weeks and 3 months, respectively.

Researchers have validated the RIFLE criteria in numerous patient populations, and the criteria have proven useful in prognosis for AKI. For example, we found that at our institution, more than 12 % of patients with a baseline creatinine level less than 1.5 mg/dL upon admission to the intensive care unit had AKI. After multivariate analysis, the risk, injury, and failure categories of AKI were associated with increases in risk of death within 60 days after intensive care unit admission by 2.3-, 3.0-, and 14.0-fold, respectively. In patients with acute leukemia starting induction chemotherapy, the estimated mortality rate increased progressively within 8 weeks for the no-AKI, risk, injury, and failure categories (3.8 %, 13.6 %, 19.6 %, and 61.7 %, respectively). Small increases in serum creatinine level are closely associated with increased mortality rates and must be recognized early by physicians to prevent further deterioration of renal function. Therefore, identification and treatment of early-stage AKI (i.e., the risk category in the RIFLE criteria) at presentation is crucial.

Upon presentation at an emergency center, a thorough clinical examination and hemodynamic optimization are imperative for patients with AKI. Orthostatic hypotension, tachycardia, poor skin turgor, dry mucous membranes, and low central venous pressure suggest volume depletion, so intravenous (IV) hydration should be administered until the patient appears to be clinically euvolemic. A blood urea nitrogen:serum creatinine ratio greater than 20, fractional excretion of sodium less than 1 %, a urine sodium level less than 20 mEq/L, and the presence of hyaline casts in urinalysis suggest prerenal azotemia. Fractional excretion of sodium greater than 2 %, a urine sodium level greater than 40 mEq/L, and the presence of coarse granular casts in urinalysis are more suggestive of acute tubular necrosis. Urinary obstruction is generally indicated by hydronephrosis in ultrasonography, although hydronephrosis may not develop in patients with significant retroperitoneal disease. Patients with severe bladder outlet obstruction may have a palpable bladder. In diagnosis of urinary obstruction or retention, use of a portable bladder scanner may confirm an elevated postvoid residual urine volume (greater than 50–100 mL).

The optimal fluid-based therapy for AKI, especially in patients with sepsis, has been a subject of much debate. IV albumin may be given, but it has not proven to be more effective than crystalloid solutions. Other colloids, such as IV starch, are directly injurious to the kidney in that they cause osmotic nephrosis of the renal tubules; thus, in general, their use should be avoided in patients with AKI. In addition, albumin and starch leak out of the intravascular compartment within hours after administration, thereby potentially worsening peripheral edema. We generally prefer using crystalloid solutions such as isotonic saline (0.9 % saline) for volume resuscitation. Patients with sepsis have systemic vasodilation that contributes to hypotension and, likely, the need for vasopressor support. Continuous infusion of norepinephrine (2–12 μg/min) or vasopressin (0.01–0.04 U/min) is generally used to achieve a target mean arterial pressure of 70 mm Hg to preserve perfusion of vital organs. Placement of a Foley catheter should be attempted 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. Use of nephrotoxic medications and iodinated contrast agents should be avoided, if possible.

Currently, an effective therapy for AKI does not exist, and supportive dialysis may be necessary until AKI resolves. Some patients with AKI who present to an emergency center may urgently need dialysis. These are patients with uncontrollable hyperkalemia, extreme fluid overload, severe metabolic acidosis, uremia, or marked tumor lysis syndrome (TLS). Early nephrology consultation in the emergency center would facilitate dialysis in these patients in a timely manner. Intermittent hemodialysis is generally sufficient for volume and metabolic clearance. However, patients with septic shock or severe TLS may need continuous renal replacement therapy. We have found that continuous, sustained low-efficiency dialysis in the intensive care unit provides optimal metabolic clearance and minimizes the cumulative positive fluid balance in patients who are hemodynamically unstable.

Multiple Myeloma and AKI

Multiple myeloma is a neoplastic disorder of plasma cells that results in the overproduction of monoclonal immunoglobulins and fragments (paraproteins). These paraproteins circulate in the bloodstream and may deposit in vital organs, leading to tissue injury. AKI is a common manifestation of paraprotein deposition in the kidneys. Classic myeloma cast nephropathy develops when paraproteins filter through the glomeruli and bind to Tamm-Horsfall mucoprotein in the distal tubule, leading to cast formation and tubular obstruction. Another manifestation is immunoglobulin light chain amyloidosis (primary amyloidosis), in which paraproteins undergo conformational changes and deposit as amyloid fibrils in the glomeruli and vasculature. Lastly, light chains may deposit within the glomerular and tubular basement membranes, leading to light chain deposition disease.

The clinical presentation of AKI in patients with multiple myeloma may be insidious, with only mild proteinuria or severe proteinuria with fulminant renal failure. More than half of all patients with multiple myeloma present with some degree of AKI, and 10 % of them need dialysis. Physicians must consider occult multiple myeloma in elderly patients who have acute or chronic kidney disease with no obvious etiology. Initial work-up for multiple myeloma consists of serum and urine protein electrophoresis to detect elevated levels of monoclonal proteins. Serum-free light chain assays are now widely available, and use of them has increased the sensitivity of detection of monoclonal proteins in serum. Routine qualitative dipstick urinalysis, which detects albuminuria, does not detect monoclonal proteins (Bence Jones proteins). Light chain deposition disease and amyloidosis cause glomerular damage, leading to significant albuminuria. In contrast, classic myeloma cast nephropathy spares the glomeruli, and patients with it typically present with only mild albuminuria. Patients with amyloidosis may also present with systemic manifestations such as restrictive cardiomyopathy, hepatomegaly, carpal tunnel syndrome, and orthostatic hypotension. Renal biopsy analysis reveals light chain or amyloid deposits, which provides the definitive diagnosis.

Patients who present with multiple myeloma and renal disease must undergo aggressive treatment to preserve kidney function. Initial hydration consists of infusion of normal saline, with a urine output goal of 2.5–3.0 L a day, which helps prevent the formation of casts. Therapy aimed at decreasing the production of paraproteins (i.e., steroids) should be instituted immediately to alleviate end-organ damage. Use of concomitant nephrotoxic medications reportedly potentiates renal injury. Use of aminoglycosides, IV contrast agents, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided. Hypercalcemia commonly occurs in patients with multiple myeloma. Although the risk of acute tubular necrosis is low, therapy with a bisphosphonate should be considered if hypercalcemia does not resolve with the use of hydration, loop diuretics, and calcitonin (3–4 mg of zoledronic acid diluted in 100 mL of normal saline administered in an IV infusion for at least 15 min). A large randomized controlled trial of plasmapheresis in the setting of AKI secondary to myeloma did not demonstrate a significant improvement in the composite endpoint of death, dialysis dependence, and glomerular filtration rate less than 30 mL a minute. Use of high cutoff filters for rapid removal of light chains via hemodialysis may be more effective than plasmapheresis and is currently being studied in Europe.

Electrolyte Abnormalities

TLS

TLS can be a life-threatening emergency in patients with cancer. Massive tumor-cell breakdown releases potassium, phosphorus, and uric acid into the extracellular environment, which overwhelms the excretory capacity of the kidneys. Hyperkalemia may predispose patients to cardiac arrhythmias and sudden death. Hyperphosphatemia and secondary hypocalcemia may lead to muscular irritability, cardiac arrhythmias, and metastatic calcification. Uric acid may precipitate in the renal tubules and cause AKI. TLS generally occurs in patients receiving chemotherapy, although it can occur spontaneously.

Patients with rapidly proliferating 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 tumor, advanced age, and chronic kidney disease. Although patients with lymphoma or acute leukemia are at greatest risk, authors have reported cases of TLS in patients with a variety of solid tumors undergoing chemotherapy and/or radiation therapy.

Identification of TLS is fairly straightforward in a patient who presents with marked derangements in electrolyte levels. The diagnosis may be less clear in patients in whom AKI is secondary to an effective prerenal state, such as volume depletion or hypotension. Similar to patients with TLS, these patients may have hyperkalemia, hyperphosphatemia, and hyperuricemia. In the absence of other risk factors for TLS, these patients generally experience improvement in electrolyte levels and renal function with hydration or normalization of blood pressure.

Management of TLS largely consists of maintaining adequate urine output to facilitate excretion of potassium, phosphorus, and uric acid. Infusion of isotonic saline should be instituted 24 h prior to chemotherapy at 80–100 mL/m^2 an hour and titrated accordingly to maintain a urine output of at least 2.5 L a day. Fluid management may be affected by underlying heart failure. Alkalinization of the urine with IV sodium bicarbonate may help prevent the formation of uric acid crystals but may increase the risk of calcium phosphate crystal deposition. Therefore, routine use of sodium bicarbonate in patients with TLS is no longer recommended.

Another important part of treatment of TLS is normalization of serum uric acid levels. Traditional treatment of hyperuricemia included daily administration of allopurinol (100–300 mg orally or intravenously) to decrease the production of uric acid. Unfortunately, allopurinol may be ineffective in patients with massive cell lysis. Rasburicase (0.2 mg/kg [IV] daily for up to 5 days) converts uric acid into readily excreted allantoin and was recently approved for the prevention and treatment of hyperuricemia. Serum uric acid levels often decrease until they become undetectable after rasburicase-based treatment. Whether this more pronounced hypouricemic effect of rasburicase than of allopurinol translates into improved renal and patient outcomes is unknown.

Patients with TLS who have electrocardiogram abnormalities, arrhythmias, or oliguria should be evaluated immediately by a nephrologist for renal replacement therapy. Use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and NSAIDs should be avoided because they may cause hyperkalemia and reduce glomerular filtration. Prophylactic dialysis is not recommended for patients with TLS or isolated hyperuricemia in the absence of AKI.

Hyponatremia

Authors have reported hyponatremia in 3.8 % of patients in emergency centers, although its incidence in cancer patients presenting to emergency centers is not known. The reported frequency of hyponatremia in patients admitted to hospitals based on a serum sodium level less than 135 mEq/L varies widely, ranging from 5.5 % to 28.0 %. In our institution, we found that 48 % of hospitalized patients had serum sodium levels less than 135 mEq/L. Increased hyponatremia severity was closely associated with increased length of hospital stay and 90-day mortality rate. The most common 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., lung, gastrointestinal, central nervous system), pneumonia, use of certain drugs (e.g., antidepressants, haloperidol, carbamazepine, cyclophosphamide, vincristine), nausea, and pain. Renal salt wasting resulting from chemotherapy, "tea and toast syndrome" resulting from malnutrition, and adrenal insufficiency resulting from metastasis or steroid withdrawal should be considered when assessing patients with hyponatremia.

Patients with hyponatremia may present with mild symptoms such as confusion, dizziness, nausea, and lethargy. Severe symptoms include seizures, coma, and death. The occurrence of symptoms of hyponatremia depends primarily on the rate of decline of the serum sodium level as opposed to its actual measured level. The brain is able to adapt to hyponatremia by excreting osmolytes from cells to prevent cerebral edema. If the rate of decline in the serum sodium level outpaces the excretion of osmolytes, cerebral edema with eventual herniation of the brain stem may develop. This requires immediate treatment 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. Immediate treatment is not indicated in this situation.

Initial work-up 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 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 will also 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 diluted urine (urine osmolality less than plasma osmolality). Finally, patients with tea and toast syndrome or malnutrition have serum sodium levels less than 20 mEq/L along with diluted urine.

Hyponatremic patients who are asymptomatic or have mild symptoms generally do not need immediate treatment. Rapid correction of hyponatremia in these patients will increase the risk of osmotic demyelination syndrome. If patients have volume depletion, they should receive isotonic fluids such as normal saline. Otherwise, fluid administration should be restricted to less than 1 L a day. Salt tablets may be given to patients without hypervolemia (initially, 1 g 3 times a day). The introduction of vasopressin receptor antagonists 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 stimulating water diuresis. Oral tolvaptan (7.5–15.0 mg daily) or IV conivaptan (20-mg loading dose with 20 mg administered over the ensuing 24 h) may be given with close monitoring of the sodium correction rate.

Treatment of hyponatremia in patients with severe symptoms consists of infusion of 3 % saline at a rate of 0.6–1.0 mL/kg an hour and initial monitoring of serum sodium levels at least every 2–4 h. The infusion is continued until the sodium level is greater than 120 mEq/L, symptoms have resolved, or the rate of sodium level correction exceeds 8 mEq within 24 h. Rates of correction in excess of 10–12 mEq per 24 h have been associated with osmotic demyelination syndrome, which may result in altered mental status, quadriparesis, quadriplegia, pseudobulbar palsy, coma, or death. Therefore, vigilant monitoring of serial sodium levels with titration of the 3 % saline infusion to prevent overcorrection of hyponatremia is necessary.

Hyperkalemia

Hyperkalemia is a particular concern in patients presenting to emergency centers, as it can be life-threatening. Common causes of hyperkalemia in patients with cancer include AKI, TLS, 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. Progressive electrocardiographic changes include peaked T waves, absence of P waves, widened QRS complexes, and, eventually, sine waves. Severe hyperkalemia may cause significant skeletal muscle weakness. The first step in the treatment of hyperkalemia is stabilization of the myocardial membrane with IV administration of calcium gluconate or calcium chloride (2 g over 5 min). The dose may be reinfused until electrocardiographic changes resolve. The second step is shifting of potassium to the intracellular space with regular administration of insulin (10 U), glucose (50 mL of 50 % dextrose), and inhaled beta-agonists. Sodium bicarbonate administration will also help in patients with concurrent metabolic acidosis but will not correct hyperkalemia in patients without acidosis. Although sodium polystyrene sulfonate is commonly given to aid in potassium elimination from the gut, its clinical effectiveness is unproven in clinical studies, and its use has been associated with intestinal necrosis. If severe hyperkalemia persists despite correction of its underlying cause, dialysis may be necessary. For patients with milder hyperkalemia in the absence of T waves, monitoring serial potassium levels after discontinuation of the causative drug may be sufficient. Loop diuretics may be administered to patients with adequate renal function to enhance potassium excretion in the urine.

Urinary Diversions

John Simon performed the first urinary diversion in 1852 by creating a ureterorectal anastomosis in a patient with bladder exstrophy. Subsequently, ureterosigmoidostomy became the procedure of choice in the early 1900s, but it was complicated by reflux nephropathy, metabolic acidosis, hypokalemia, and a high incidence of cancer at the anastomosis site. Physicians developed conduits using bowel segments as urine reservoirs with continuous drainage into a urostomy bag from a stoma in the abdominal wall in the 1950s; conduits used with the ileum had lower incidences of metabolic abnormalities than did those used with the jejunum. More recently, researchers developed neobladders with urinary excretion via a stoma in the abdominal wall or internally via the urethra. Unlike patients with conduits, those with neobladders do not suffer from incontinence, but they may need intermittent self-catheterization.

The intestinal epithelium is normally involved in secretion of sodium and bicarbonate and reabsorption of ammonia, ammonium, hydrogen, and chloride. Therefore, patients with bowel conduits are at risk for hyperchloremic metabolic acidosis secondary to bicarbonate loss in the urine. This risk is increased in patients with large bowel surface areas in the conduits, increased urine-conduit contact times, jejunal (versus ileal) conduits, or chronic kidney disease. If large segments of the ileum or colon are resected to make a conduit, the patient may experience diarrhea caused by bile salt malabsorption and secretion of chloride and water into the bowel lumen. This may further exacerbate electrolyte abnormalities. Physicians should monitor patients who have undergone ileal or stomach resection for conduit or neobladder creation for macrocytic anemia secondary to vitamin B_{12} deficiency. In rare cases, reabsorption of ammonia in patients with chronic liver disease may lead to altered mental status. Metabolic abnormalities are uncommon in patients with urinary diversions created from the stomach because the gastric mucosa is relatively impermeable. However, metabolic alkalosis may develop in patients with chronic kidney disease secondary to H^+ secretion from the gastric lining (and subsequent bicarbonate retention).

The work-up for patients with urinary diversions includes serum electrolyte, blood urea nitrogen, creatinine, calcium, and phosphorus measurements; a complete blood count; and urinalysis. Patients with chronic metabolic acidosis may present with nausea, vomiting, and decreased appetite. Volume depletion may occur secondary to decreased oral intake and diarrhea. Altered mental status may indicate significant ammonia absorption (especially in patients with pre-existing liver disease) or vitamin B_{12} deficiency. Macrocytic anemia as well as paresthesia may also suggest vitamin B_{12} deficiency.

Acidosis and volume depletion are best treated with a continuous bicarbonate infusion (1 L of sterile water with 150 mEq of sodium bicarbonate). Correction of acidosis decreases serum potassium levels; therefore, potassium should be given to patients who have hypokalemia prior to bicarbonate administration. Mild acidosis that can be managed on an outpatient basis can be treated with oral supplementation of sodium bicarbonate (650-mg tablets equaling 7.7 mEq of bicarbonate or 1 mL of sodium citrate/citric acid [Bicitra] equaling 1 mEq of bicarbonate). Measurement of the vitamin B_{12} level should be performed in patients with urinary diversions who present with unexplained macrocytic anemia. Metabolic alkalosis caused by gastric urinary diversions in patients with chronic kidney disease responds well to treatment with H_2 blockers and proton pump inhibitors.

Hematuria

Hematuria is common in patients with cancer and has various presentations, ranging from insidious to life-threatening. Microscopic hematuria is defined as more than 3 red blood cells per high-power field, whereas gross hematuria is defined as visible discoloration of the urine because of the presence of blood. In the general population, 5 % of patients with microscopic hematuria and up to 40 % of patients

Table 6.3 Common causes of hematuria in patients with cancer

Primary neoplasm
Urothelial
Renal
Prostate
Hemorrhagic cystitis
Chemotherapy (cyclophosphamide, ifosfamide)
Viral (BK virus, adenovirus, cytomegalovirus)
Radiation therapy
Coagulopathy
Factor deficiency
Disseminated intravascular coagulation
Systemic anticoagulation
Glomerulonephritis
IgA nephropathy
Postinfectious
Membranoproliferative
Pauci-immune (anti-nuclear cytoplasmic antibody disease or anti-glomerular basement membrane disease)
Thin basement membrane disease
Interstitial nephritis
Nephrolithiasis
Hypercalciuria (myeloma, bone metastases, parathyroid malignancy)
Hyperuricosuria (high cell turnover)
Infection
Cystitis
Prostatitis
Urethritis
Pyelonephritis

with gross hematuria have an underlying malignancy of the genitourinary tract. Common causes of hematuria in patients with cancer are listed in Table 6.3. Patients with cancer generally have hematuria secondary to their underlying malignancies or chemotherapy. Patients with indwelling catheters or stents may have increased predisposition to hematuria if they have thrombocytopenia or clotting deficiencies. Physicians should have a high level of suspicion of a viral etiology in patients who recently underwent hematopoietic stem cell transplantation (HSCT).

The initial work-up for patients with microscopic hematuria includes urinalysis and a complete blood count to exclude an underlying bacterial infection. Patients with excruciating unilateral colicky flank pain radiating to the groin should undergo a computed tomography scan of the abdomen and pelvis (stone protocol) to exclude underlying urolithiasis. Patients with urolithiasis less than or equal to 6 mm in diameter may excrete the stone in their urine spontaneously and may be monitored as outpatients with treatment with oral narcotics if clinically stable. Patients with

urolithiasis greater than 6 mm in diameter generally must be admitted as inpatients and undergo IV hydration, treatment with narcotics, and a urology consultation. The presence of proteinuria, de novo hypertension, or unexplained renal failure may suggest underlying glomerulonephritis in patients with hematuria, and a renal biopsy may be necessary to look for glomerular disease. Gross hematuria commonly suggests a bladder pathology such as cancer or cystitis. Patients with severe hematuria may present with hemodynamic instability and need IV hydration and administration of blood products.

Hemorrhagic Cystitis

Hemorrhagic cystitis generally develops as acute onset of bladder inflammation with gross hematuria. Most cases of hemorrhagic cystitis in patients with cancer are secondary to chemotherapy, radiation injury to the urothelium, or viral infection. In particular, the chemotherapeutic agents cyclophosphamide and ifosfamide are metabolized into acrolein, which provokes mucosal edema, hyperemia, and friability of the bladder wall within 4 h after IV exposure. For prophylaxis of hemorrhagic cystitis, sodium 2-mercaptoethanesulfonate (mesna) is administered prior to chemotherapy and binds to acrolein to form a nontoxic ester. To be effective, mesna must be present in the bladder at the time acrolein comes into contact with the urothelium. Treatment with mesna has markedly reduced the incidence of hematuria and hemorrhagic cystitis following cyclophosphamide-based chemotherapy to less than 5 %. Aggressive IV hydration with forced diuresis to dilute urinary acrolein and minimize the contact of acrolein with the urothelium is also successful in preventing cystitis.

Patients with acute radiation cystitis experience symptoms during treatment and present with dysuria and urinary urgency and frequency. Damage to the bladder mucosa leads to acute inflammation and tissue edema. Symptoms may last for up to 3 months and are generally self-limited, as the bladder mucosa divides rapidly. Treatment is largely limited to symptom management and includes anticholinergic drugs and phenazopyridine. In comparison, late radiation cystitis may develop 6 months to 20 years after radiation therapy and is a manifestation of damage to slowly dividing vascular and connective tissue. Subsequent ischemia, hypocellularity, and fibrosis lead to sloughing of the mucosal surface and hematuria. Other potential complications of radiation cystitis include ulcer and fistula formation. The degree of injury in patients with chronic radiation cystitis is related to the cumulative radiation dose and intensity of radiation therapy. Physicians have used hyperbaric oxygen therapy for radiation cystitis to overcome ischemic injury, but it is not routinely available in all centers.

The most common viruses associated with cystitis in patients with cancer include BK virus (a member of the polyomavirus family), adenovirus, and cytomegalovirus. Viral urinary tract infections (UTIs) should be strongly considered in the differential diagnosis of hematuria in patients after HSCT. Symptoms of viral UTI include fever,

gross or microscopic hematuria, lower abdominal pain, dysuria, and urinary frequency and urgency. BK virus is the most common viral pathogen in patients after HSCT and may ascend the urogenital tract, leading to cystitis, ureteral strictures, and interstitial nephritis. BK virus infection is diagnosed using quantitative polymerase chain reaction analysis of blood and urine samples and according to the presence of decoy cells in urine cytology. Adenoviruria is invariably associated with cystitis, whereas BK viruria is clinically asymptomatic in 50 % of patients after HSCT. Patients with severe adenoviral infection may present with systemic disease manifesting as hemorrhagic colitis, pneumonitis, hepatitis, or hemorrhagic cystitis. Cytomegalovirus is a relatively rare cause of cystitis and can be detected using polymerase chain reaction analysis. Cidofovir is active against BK virus, adenovirus, and cytomegalovirus, but treatment with it is limited by its nephrotoxicity. Ganciclovir and foscarnet also can be used to treat active cytomegalovirus infections.

Management of hemorrhagic cystitis regardless of its etiology involves maintenance of urinary flow using IV hydration and blood transfusions, if needed. If blood clots develop in the bladder, patients may experience painful urinary obstruction. The physician must re-establish urinary flow by inserting a large-diameter 3-way transurethral catheter into the bladder and initiate manual or continuous lavage to remove the clots. If lavage at bedside is not successful, endoscopic clot evacuation under general anesthesia can be considered. Using a cystoscope, the urologist can directly visualize and disrupt clots, inspect the bladder to identify any controllable sources of bleeding, and cauterize bleeding vessels in the bladder wall. Intravesicular instillation of hemostatic agents (e.g., aluminum, placental extract, prostaglandins, formalin) may be necessary with severe hemorrhaging. A PCN also may be necessary if an obstruction caused by hematuria does not resolve.

UTI

Patients with cancer are susceptible to UTI secondary to neutropenia and chronic immunosuppression. In addition, frequent use of transurethral catheters, PCNs, and ureteral stents predisposes these patients to the formation of biofilm along the artificial surface, which interferes with normal host defenses and facilitates bacterial colonization. Catheter-associated UTIs account for 40 % of all hospital-acquired infections, and risk factors for these infections include a long catheterization duration, female sex, diabetes, advanced age, and serum creatinine level greater than 2 mg/dL. The most common organisms identified in UTI cases are *Escherichia coli*, *Klebsiella* species, *Staphylococcus saprophyticus*, *Enterobacter* species, and *Proteus* species. Common pathogens in patients with hospital-acquired UTIs include *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Candida albicans*. Patients who have diabetes, frequent UTIs, indwelling catheters, or hospital-acquired UTIs are considered to be at risk for complicated UTI and must undergo aggressive management. Other risk factors for complicated UTI include pregnancy, chronic immunosuppression, and recent antibiotic use.

The UTI incidence rate in patients with urinary diversions is 33 %. *E. coli* and *Proteus*, *Pseudomonas*, and *Enterobacter* spp. are the most frequently isolated organisms in these patients. Alkaline urine predisposes patients to bacterial proliferation. Patients with urinary diversions who present with pyelonephritis or sepsis should be evaluated for obstructions or stenosis of the diversions. Routine urine cultures are not indicated for asymptomatic patients, as the bowel used to create the diversion is normally colonized with bacteria. Treatment with antibiotics should be considered for patients with urinary diversions who present with unexplained fever, cloudy urine, flank pain, or hematuria.

Symptoms of a lower UTI (cystitis) include dysuria, urinary frequency, acute hematuria, and suprapubic or pelvic pain. Patients with an upper UTI (pyelonephritis) may present with nausea or vomiting, flank pain, fever, rigor, and altered mental status. Urinalysis may be positive for bacteruria (100–1000 cfu of bacteria/mL), pyuria (at least 10 leukocytes/mL), leukocyte esterase, and nitrite. A transurethral catheter-associated UTI is indicated by the presence of clinical symptoms (e.g., fever, rigor, altered mental status, lethargy, flank pain, acute hematuria, decreased blood pressure, metabolic acidosis) and a urine culture with at least 10^3 cfu of bacteria per milliliter. For patients with indwelling urinary catheters, treatment of asymptomatic bacteruria is not required unless the patient is pregnant or undergoing a urologic procedure with expected mucosal bleeding. In addition, pyuria alone is not diagnostic for catheter-associated UTIs. Urine cultures are not routinely obtained for suspected uncomplicated cystitis but are suggested for treatment of persistent UTIs despite previous treatment or the presence of complicated cystitis, a catheter-related UTI, or pyelonephritis. Imaging studies for UTIs are generally not warranted unless a urinary obstruction or abscess is suspected.

Initial empiric antibiotic therapy for UTIs should be selected based on patient allergies, the presence of bacterial resistance, and cost. Treatment of uncomplicated acute cystitis includes oral administration of nitrofurantoin (100 mg twice a day for 5 days) or trimethoprim-sulfamethoxazole (160–800 mg twice a day for 3 days). If these agents are contraindicated, then a fluoroquinolone (3-day course) or beta-lactam (amoxicillin-clavulanate, cefdinir, or cefpodoxime proxetil; 3- to 7-day course) may be considered. For complicated cystitis, a 7- to 10-day course of an oral fluoroquinolone is suitable. If parenteral therapy is warranted, agents such as fluoroquinolones, ceftriaxone, and aminoglycosides can be given once daily. Patients with catheter-associated UTIs should undergo replacement or removal of the catheter and receive a fluoroquinolone or cephalosporin for 7–14 days. If *Pseudomonas* infection is suspected, the patient should receive ciprofloxacin, ceftazidime, or cefepime. Vancomycin is appropriate for Gram-positive coccal infections until antibiotic susceptibility is determined. For pyelonephritis not requiring hospitalization, an oral fluoroquinolone (7-day course) or trimethoprim-sulfamethoxazole (14-day course) is appropriate. An initial 1-time IV loading dose may be given prior to discharge from the emergency room (e.g., 1 g of ceftriaxone, 24-hour dose of an aminoglycoside). For patients with pyelonephritis requiring hospitalization, appropriate IV antibiotics include fluoroquinolones, aminoglycosides with or without ampicillin, extended-spectrum cephalosporins, penicillins with or

without an aminoglycoside, and carbapenems. For all UTIs, the antibiotic regimen should be tailored to the final antibiotic sensitivities as determined in urine culture. Patients with UTIs who are neutropenic (absolute neutrophil count <1500/μL) should be given treatment according to neutropenic guidelines.

Obstructive Uropathy

Obstructive uropathy is the impedance of normal urine flow anywhere from the renal tubule to the urethra. The resulting increase in intraluminal pressure generally occurs with hydroureter and hydronephrosis and may be unilateral or bilateral depending on the location of the obstruction. If left untreated, irreversible loss of kidney function will eventually occur. Common causes of obstructive uropathy in cancer patients are listed in Table 6.4. Primary tumors of the prostate, bladder, uterus, and cervix account for more than 70 % of malignancy-associated obstructions. The most likely cause of a urinary tract obstruction within 2 years after radiation therapy is a recurrent tumor; thereafter, the most common cause is radiation-induced fibrosis.

Table 6.4 Common causes of obstructive uropathy in patients with cancer

Upper urinary tract obstruction
Primary malignancy
Renal pelvis
Ureter
Ovary
Retroperitoneal disease
Metastatic cancer (cervix, bladder, breast, colon, ovary, prostate)
Lymphoma
Sarcoma
Fibrosis (idiopathic, radiation)
Ureteral strictures (radiation, polyoma virus)
Ureteral encasement (lymphadenopathy)
Urolithiasis
Lower urinary tract obstruction
Primary malignancy
Cervix
Uterus
Prostate
Bladder
Urinary retention
Medications (anticholinergics/antispasmodics, antihistamines, tricyclic antidepressants)
Spinal cord injury caused by vertebral metastases
Bladder calculus
Blood clots (hemorrhagic cystitis)
Fungus ball

The clinical presentation of obstructive uropathy varies depending on whether the obstruction is (1) unilateral or bilateral, (2) acute or chronic, and (3) complete or partial. Acute obstructive uropathy may manifest as acute flank or suprapubic pain and worsening hypertension, whereas chronic obstructive uropathy symptoms may be more vague or completely absent. Patients with partial obstruction of the bladder or ureters may have polyuria, nocturia, and urinary frequency, whereas patients with bilateral complete obstruction may have anuria. Also, patients may have a palpable flank or suprapubic mass with tenderness upon clinical examination. Laboratory test results may be essentially normal in patients with unilateral disease if the unobstructed kidney is healthy. Abdominal ultrasonography is sensitive in detecting hydronephrosis, hydroureter, and filling defects in the bladder. However, ultrasonography may miss obstructions in patients with significant retroperitoneal disease or ureteral encasement, both conditions that may prevent dilation of the urinary tract. If ultrasonography is suggestive of an obstruction or clinical suspicion of an obstruction is high, a computed tomography scan using a stone protocol may help identify the site and delineate the cause of the obstruction. Also, isotope renography may be used to identify functional obstructions in indeterminate cases of obstructive uropathy. Using a portable bladder scanner, a physician can quickly determine whether a patient has a significant amount of postvoid residual urine (greater than 50–100 mL), which is suggestive of urinary retention or obstruction.

The first step in management of obstructive uropathy at the level of the bladder outlet is passing a small (14 French) urethral catheter into the bladder. In the male patient, a Foley catheter should be passed into the bladder to its hub, and urine return should be verified before inflating the balloon. This will prevent inadvertent inflation of the balloon in the prostatic urethra, which could cause mucosal laceration and bleeding. Patients with rectal, gynecologic, or genitourinary tumors are at particular risk for iatrogenic bleeding or lacerations when using urethral catheters. Care should be taken to avoid forcing a Foley catheter that is not passing easily into the bladder because of the risk of posterior urethral lacerations or even tears under the prostatic capsule, which may lead to extravasation of urine into the pelvis and perineum. This may rapidly progress to urosepsis and soft tissue infection.

Patients with obstructions above the level of the bladder may have to undergo decompression of the collecting system via placement of a ureteral stent or PCN. Subsequent management includes replacement of the stent or PCN every 3 months. Ureteral decompression in cancer patients is associated with increased morbidity and decreased quality of life. Complications include infection, stent migration, pain at the insertion site, bladder spasms, recurrent obstruction, and leakage. Ureteral stents eventually fail in 16–58 % of patients with malignancies. PCN placement has not proven to markedly improve survival rates in patients with advanced cancer and may adversely affect quality of life. However, ureteral decompression may be more valuable in patients with stone disease, ureteral strictures, and/or hemorrhagic cystitis. In the cancer setting, consideration of the patient's prognosis before decompression of the ureters is important. Placement of a stent or PCN may be justified to improve renal function for further cancer therapy, alleviate pain, or prevent the need for dialysis or as part of treatment of urosepsis.

Key Practice Points

- The RIFLE 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.
- More than half of all patients with multiple myeloma will initially present with some degree of renal injury, and AKI may improve 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.
- Urinary diversions created from bowel segments are often complicated by the development of chronic metabolic acidosis, hypokalemia, volume depletion, and vitamin B_{12} deficiency.
- Hemorrhagic cystitis commonly results from cyclophosphamide administration, radiation therapy, and viral infection after HSCT. Management of hemorrhagic cystitis includes IV fluids, bladder irrigation, antiviral drugs, and urologic consultation.
- UTIs are common in patients with cancer owing to underlying neutropenia, use of chronic indwelling devices (transurethral catheters, ureteral stents, and PCNs), and creation of urinary diversions using bowel segments.
- Obstructive uropathy is a common complication of pelvic malignancies and generally requires intervention with a transurethral or suprapubic catheter, ureteral stent, or PCN.

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Chapter 7
Rheumatologic/Orthopedic Emergencies

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Contents

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Chapter Overview

Patients with cancer frequently present with signs and symptoms of musculoskeletal and rheumatic diseases. Acute joint pain with swelling is the most common indication of an emergency rheumatologic evaluation. Individuals with monoarthritis should be evaluated immediately to rule out septic arthritis, as patients with cancer are at high risk for infection because of the immunosuppressive effects of their cancer and its treatment. Furthermore, use of empiric broad-spectrum antibiotics should be initiated to prevent loss of joint function. Acute crystal-induced arthritis—either gout or calcium pyrophosphate crystal deposition (CPPD) disease—is one of the most common causes of painful, swollen joints in patients with cancer and is often triggered by dehydration. Paraneoplastic syndromes can present as oligoarthritis or polyarthritis and are often diagnoses of exclusion. Other rheumatologic paraneoplastic syndromes, such as myositis, vasculitis, and tendinitis/fasciitis, can lead to significant morbidity. Skeletal complications may be caused by local or metastatic tumor invasion, pathologic and osteoporotic fractures and osteonecrosis; and are usually associated with severe pain. In addition, cancer patients with preexisting rheumatologic diseases can experience flare-ups of those diseases that require urgent intervention. All of these scenarios require physicians to be able to recognize the indications for emergency evaluation and treatment to prevent complications and ensure that patients continue to benefit from optimal cancer treatment.

Introduction

Musculoskeletal symptoms are common indications for office visits. Such symptoms in cancer patients can be the first signs of an emergency condition that requires immediate evaluation and intervention to prevent compromise of their cancer treatment or potentially life-threatening outcomes. Primary care physicians, emergency room staff, and oncologists are on the front line of evaluation of such patients. Being able to identify such conditions and provide the initial work-up for proper differential diagnosis and treatment in a timely manner is vital to preserving function and prolonging survival. This chapter is focused on the common bone, joint, and muscle symptoms in cancer patients.

Arthritis

Joint pain with swelling is the most common indication for rheumatologic evaluation in the emergency setting. Pain in a joint must be distinguished from pain in the adjacent soft tissue. Arthritis is associated with joint swelling, pain, and decreased

range of motion, whereas soft tissue pain and swelling around the joint can be palpated, extending beyond the joint and often leaving the range of motion of the joint unaffected. Arthritis can occur in a single joint (monoarthritis), a few joints (oligoarthritis), or multiple joints (polyarthritis).

Monoarthritis

Causes of acute monoarthritis can overlap with those of oligoarthritis and polyarthritis. However, a cancer patient presenting with a single hot, swollen, tender joint with restricted range of motion has a true rheumatologic emergency, as cancer patients often undergo immunosuppressive treatment, which predisposes them to septic arthritis. If left untreated, the infection can lead to rapid destruction of the joint and irreversible loss of function. Therefore, the initial work-up for monoarthritis should focus on evaluation for a possible infection with imaging and joint fluid aspiration. Main differential diagnoses include crystal-induced arthritis, osteonecrosis, flare-up of osteoarthritis, and direct involvement of bone malignancies near joints.

Septic Arthritis

The true incidence of septic arthritis in patients with cancer is unknown. Individuals with cancer and those undergoing active treatment of cancer are at increased risk for septic arthritis because they may have indwelling catheters, open wounds from invasive procedures, or decreased immune function induced by their cancer or its treatment. Glucocorticoids, which are frequently given to patients with hematologic malignancies, can depress immunity, lower neutrophil synovial counts, and reduce function. Non-cancer-related causes of septic arthritis include pre-existing joint disease that predisposes the joint to bacterial colonization, history of rheumatoid arthritis, and diabetes mellitus.

The most commonly infected joint is the knee, although other joints can be involved, including the shoulder, wrist, and ankle and finger joints. The affected joint is usually swollen, warm, and tender. *Staphylococcus aureus* is the most common infecting pathogen; streptococci and gram-negative bacilli are also common.

Bacterial infection of joints can be the initial presentation of acute leukemia, especially in children, or a complication of leukemia treatment. Authors also have reported septic arthritis in patients with multiple myeloma. In a case study of 17 patients in whom acute infection was the first manifestation of multiple myeloma, 35 % of the patients had septic arthritis, mostly involving the knee. *Streptococcus pneumoniae* was isolated from two thirds of the patients, and bacteremia was common. The risk of infection in patients with multiple myeloma is highest during the first months after initial diagnosis and in those with renal dysfunction. Of interest, patients with colon cancer can have septic arthritis caused by *Clostridium septicum*, which can be the initial manifestation of their malignancy. Radiation therapy is

implicated to play a causative role in the development of septic arthritis in adjacent joints, such as septic arthritis of the hip joint after radiation therapy for cervical carcinoma or of the shoulder or sternoclavicular joint after radiation therapy for breast carcinoma.

Patients with hematologic malignancies are also at risk for invasive fungal infections in joints, which are most common in those with acute myeloid leukemia. *Candida* species are clinically significant pathogens in these patients. Cancer patients who experience neutropenia and candidemia have much higher rates of visceral dissemination and mortality than do patients who do not have these complications. Chronic disseminated candidiasis is most often observed in neutropenic patients with hematologic malignancies. Other risk factors for fungal infection are similar to those for bacterial infection.

The overall incidence of fungal arthritis has decreased significantly owing to the prophylactic use of fluconazole in neutropenic patients. However, fungal infections with non-*albicans Candida* spp. such as *Candida krusei*, which is resistant to treatment with fluconazole, have become more common over the past decade. Clinically, molds can be the infecting pathogens for fungal arthritis but at a lower frequency than with fungi. These molds include *Aspergillus fumigatus*, non-*fumigatus Aspergillus* species, unspecified *Aspergillus* spp., *Fusarium* species, zygomycetes, *Scedosporium apiospermum*, and *Exserohilum* species.

Atypical mycobacterial infection is a concern for immunocompromised patients. *Mycobacterium haemophilum* is emerging as an infecting pathogen in patients with acquired immunodeficiency syndrome or hematologic malignancies and recipients of organ or bone marrow transplants. Of 23 patients infected with *M. haemophilum* reported in a single institution over 10 years, all but 1 had known underlying immunosuppression. Four patients had septic arthritis or osteomyelitis. Initial atypical mycobacterial staining is often unrevealing, and specimens should be cultured for up to 8 weeks because of the slow growth of these pathogens. Once confirmed, treatment should be started accordingly.

Crystal-Induced Arthritis

A significant differential diagnosis for a single red, swollen, tender joint is crystal-induced arthritis. The most common crystal precipitation in a joint involves monosodium urate. Although the first metatarsophalangeal joint in the big toe is commonly involved, acute gouty arthritis can occur in a single joint in a finger, in the knee, or in the elbow. Involvement of multiple joints also can occur, especially in patients with a history of gout.

Clinically, patients complain of acute onset (over 6–12 h) of intense joint pain, redness, warmth, and swelling. Concurrent serum uric acid levels can be within normal limits in these patients and do not eliminate gout as a diagnosis. Acute onset of gouty arthritis can be caused by increased systemic production of uric acid after a change in diet or accelerated purine breakdown after cancer treatment or by decreased secretion of uric acid caused by impaired renal function. Other risk

factors include dehydration, immobilization, previous joint injury, and history of osteoarthritis.

In elderly patients with rapid onset of pain and swelling in a joint and no prior history of gout or hyperuricemia, the diagnosis may be CPPD disease caused by calcium pyrophosphate dehydrate deposition in the joint. The most commonly affected joints are the knees, wrists, and shoulders. CPPD crystals can be observed in the synovial fluid. Detection of chondrocalcinosis on X-rays supports this diagnosis. Although chondrocalcinosis is often asymptomatic, dehydration or prolonged immobilization can cause progression to arthritis from CPPD disease.

Arthritis Associated with Malignancy

Authors have reported direct involvement of arthritis in one or a few joints in both patients with primary non-Hodgkin lymphoma and patients with leukemia, particularly children with leukemia. Researchers have made similar observations in adult patients at our institution. Clinically, the involved joints are red, warm, swollen, and tender, mimicking the symptoms of septic arthritis. Magnetic resonance imaging can demonstrate typical lesions involving the bone and joint. Primary non-Hodgkin lymphoma also can involve the lumbar vertebral bodies, leading to radicular compression or cauda equina syndrome. Metastasis of solid tumors to joints is very rare, although direct metastasis of lung and thyroid cancer to a single shoulder joint has occurred; this is often associated with poor prognosis. Furthermore, authors have reported transarticular spread of Ewing sarcoma mimicking septic arthritis. In cases of direct metastasis to joints, imaging studies alone may be insufficient, and image-guided biopsy may be required for a definitive diagnosis.

Diagnosis and Treatment

When a patient presents with monoarthritis, a baseline X-ray of the affected joint should be obtained. Joint aspiration should be performed on an emergency basis, and synovial fluid analysis is the best diagnostic test to perform during the initial steps of evaluation. Blood culture should be performed if septic arthritis is suspected. Aspirated synovial fluid should be evaluated for the degree of inflammation using cell counts and differential analysis; gram, fungal, and acid-fast bacilli stains should be used to detect relevant pathogenic micro-organisms; and microscopic analysis should be performed to detect crystals. Synovial fluid also should be sent immediately for cultures for bacterial, fungal, and mycobacterial species. Synovial cell counts in neutropenic patients can be misleadingly low, especially in those with fungal or atypical mycobacterial infections. If a patient is neutropenic and has a low synovial cell count, a repeat arthrocentesis and cell count as well as micro-organism staining and adequate culturing are of paramount importance to confirming the clinical suspicion.

Because many patients with cancer have low platelet counts secondary to their underlying malignancy or its treatment, ultrasonography, if available, should be

used to guide arthrocentesis and avoid excessive needle manipulation and potential bleeding. Furthermore, ultrasonography may reveal the presence of synovial fluid before the joint aspiration or help identify the characteristics of a specific type of crystal-induced arthropathy, such as CPPD crystals in CPPD disease cases and tophi in gout cases. A suspected infection of a prosthetic joint always should be referred to an orthopedic surgeon. In a patient with a very low platelet count, needle aspiration can be performed immediately after platelet transfusion.

Ideally, treatment of suspected septic arthritis with antibiotics should be started soon after arthrocentesis. However, among patients with cancer, treatment with empiric antibiotics is often initiated before joint aspiration in those with life-threatening neutropenic fever. Information from blood cultures, urinalysis, and/or bronchial lavage can be used to adjust antibiotic treatment. Conventional antibiotics should be administered intravenously for 2 weeks or until symptoms improve and then orally for 4 weeks. A septic joint should be aspirated to dryness as often as required. Empiric antifungal treatment with voriconazole and intravenous amphotericin for coverage of non-*albicans Candida* infections should be considered for patients who have been receiving prophylactic antibiotic and antifungal treatment with fluconazole.

The conventional treatment of septic arthritis is antimicrobial therapy alone. However, a small trial in pediatric patients with septic arthritis demonstrated that short-term use (4 days) of dexamethasone at the beginning of antibiotic treatment led to markedly improved symptoms and markers of inflammation, shortened hospital stays, and no increase in adverse events. The efficacy and safety of glucocorticoids in managing septic arthritis in cancer patients must be established in formal studies.

In general, treatment of an acute gout attack should start as soon as possible after the attack begins, preferably within hours of symptom onset. Rapid, complete resolution of symptoms is associated with early treatment. Administration of an anti-inflammatory agent at a full recommended dose should be started, and the patient should continue receiving treatment for the duration of the attack, usually at a reduced dose once a significant response is observed. Several classes of anti-inflammatory agents have proven to be effective for the treatment of acute gout, including nonsteroidal anti-inflammatory drugs, colchicine, glucocorticoids, and monoclonal antibodies against inflammatory cytokines. When oral colchicine is used, hourly accelerated dosing should be avoided, as most patients experience severe diarrhea with no added benefit. Low-dose oral colchicine, with an initial dose of 1.2 mg followed 1 h later by a dose of 0.6 mg, in the first day of treatment has exhibited similar efficacy to high-dose colchicine.

The challenging issues in cancer patients with acute gout attacks include low platelet counts, renal and hepatic impairment, and polypharmacy. Use of nonsteroidal anti-inflammatory drugs should be avoided in patients with low platelet counts and impaired renal function. The colchicine dose should be lowered in patients with impaired renal or hepatic function and those concurrently taking a drug that decreases the availability of CYP3A4 to prevent toxicity. When nonsteroidal anti-inflammatory drugs and colchicine are contraindicated, treatment with systemic and

intra-articular glucocorticoids is effective. When a co-existing joint infection or skin infection overlaying the joint cannot be ruled out, intra-articular use of glucocorticoids should be avoided. Although long-term prophylaxis with oral allopurinol is usually not initiated during an acute gout attack, it may be necessary for patients anticipated to have increased purine metabolism and frequent gout attacks during chemotherapy. This can be done safely after patients receive anti-inflammatory agents and experience marked improvement of their acute symptoms. They should also continue receiving a low-dose anti-inflammatory agent to prevent further acute gout flare-ups induced by the initiation of treatment with allopurinol. Anti-inflammatory cytokines such as anti-interleukin-1 have yet to be studied extensively in cancer patients, although they are promising because of their rapid reduction of inflammation.

Oligoarthritis and Polyarthritis

A small percentage of cancer patients with septic arthritis present with polyarticular symptoms, reflecting bacteremia and diminished resistance to infection. Painful polyarthritis can be the initial sign of an undiagnosed malignancy. Oligoarthritis has occurred in patients with lung cancer as well as patients given intravesical bacillus Calmette-Guérin for bladder cancer. Although these symptoms can be self-limiting, they often necessitate additional treatment with anti-inflammatory agents, such as glucocorticoids. Polyarthritis can also be an active flare-up of a co-existing rheumatologic disease, such as rheumatoid arthritis and psoriatic arthritis, in patients with cancer. In this setting, chemotherapy for the underlying malignancy often offers good control of the arthritic symptoms of autoimmune diseases, although additional treatment with immunosuppressive drugs may be needed.

Paraneoplastic Syndrome Associated with Polyarthritis

Carcinomatouspolyarthritis is a rare paraneoplastic disorder that has been associated with a variety of solid tumors, including bronchogenic, lung, and colon cancer, and with hematologic malignancies. It is often characterized by sudden onset of asymmetric migratory arthritis involving a few joints. Large joints are involved more often than small ones. Synovitis is not associated with joint erosions, nodules, or deformities. The pathogenesis of carcinomatous polyarthritis is not well understood but is thought to involve autoimmune processes. In general, oligoarthritis and polyarthritis resolve after successful treatment of the malignancy with chemotherapy or tumor resection. For patients with significant joint pain, symptom treatment with steroid injections if just a few joints are involved or low to intermediate doses of oral glucocorticoids can offer good symptom control. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a syndrome with the typical feature of subcutaneous pitting edema that affects both hands and feet. Symmetric

polyarthritis of the peripheral joints mimics rheumatoid arthritis. However, the tenosynovitis associated with RS3PE is not associated with other typical features of rheumatoid arthritis, such as rheumatoid factor, joint erosions, and subcutaneous nodules. Pathogenically, researchers have found serum concentrations of vascular endothelial growth factor that were markedly increased in patients with active RS3PE. Vascular endothelial growth factor promotes synovial inflammation and vascular permeability in patients with RS3PE, suggesting that RS3PE can be classified as a vascular endothelial growth factor-associated disorder. RS3PE also has been associated with malignancy. In a review of the published literature, authors reported a total of 59 patients with 32 different malignancies diagnosed with RS3PE. Eighteen of these malignancies were solid tumors, including prostate cancer, gastrointestinal cancer, lung cancer, breast cancer, ovarian cancer, bladder carcinoma, endometrial cancer, cryptogenic hepatocellular carcinoma, and fibrohistocytoma, whereas 11 were hematologic malignancies, including non-Hodgkin lymphoma, leukemia, and myelodysplastic syndrome. Some patients had malignancies of unknown origin. Overall, researchers have suggested that malignancies may occur in 20–54 % of patients with RS3PE. Patients with both RS3PE and cancer often have more dramatic systemic symptoms than do patients with RS3PE alone. Also, RS3PE in the former patients is often refractory to therapy with glucocorticoids, whereas that in the latter patients is not. Signs and symptoms of RS3PE may improve after tumor removal.

Severe arthralgia associated with the use of aromatase inhibitors can occur in postmenopausal women with receptor-positive breast cancer, but it is rare. It should be considered a differential diagnosis in patients with polyarthralgia. The arthralgia usually occurs in joints that are in the distribution of osteoarthritis, such as those in the hands, knees, and shoulders, with no clear association with inflammatory arthritis features. Symptoms can be severe enough to significantly affect quality of life, leading to early discontinuation of therapy, and patients with it can present to the emergency room. In many cases, symptoms can be effectively managed with oral analgesics or other conservative strategies. Early recognition and effective management of aromatase inhibitor-induced arthralgia can help increase treatment adherence, enabling patients to experience optimal benefits of the treatment and preventing cancer recurrence.

Myositis

Myositis is inflammation of a muscle or muscle groups. Typically, patients present with pain, tenderness, swelling, and/or weakness. Possible etiologies for myositis include infection, autoimmune myositis, inclusion body myositis, adverse effects of drugs, and hereditary conditions. Infectious myositis is most often caused by bacteria, especially in immunocompromised patients. Inflammatory myopathies represent a heterogeneous group of autoimmune systemic diseases characterized by muscle weakness and inflammatory cell infiltration into skeletal muscle.

Pyomyositis

Pyomyositis is an acute intramuscular bacterial infection, usually with abscess formation. As a result of hematogenous spread, pyomyositis commonly involves a single muscle group of the lower extremity, although any muscle group can be involved. Pyomyositis is classically an infection found in the tropics, although its incidence in temperate climates has increased in recent years. Predisposing factors for pyomyositis include immunodeficiency, trauma, intravenous drug use, concurrent infection, and malnutrition. Immunodeficiencies associated with pyomyositis include human immunodeficiency virus infection, diabetes mellitus, malignancy, cirrhosis, renal insufficiency, organ transplantation, and administration of immunosuppressive agents for autoimmune diseases.

Pathogenesis

Bacteremia in the setting of muscle injury or hematoma formation is implicated to have a role in the pathogenesis of pyomyositis, although muscle trauma is documented in only 30–50 % of reported cases. *S. aureus* infection is the leading cause of pyomyositis in up to 90 % of cases in the tropics and 60–70 % of cases in temperate regions. Infection with methicillin-resistant *S. aureus*, including community-acquired strains, is on the rise in patients with pyomyositis. Group A streptococci are the second most common infecting pathogens in pyomyositis cases. Less common pathogens include non-group A streptococci, pneumococci, and gram-negative enteric bacilli.

Escherichia coli has emerged as an infectious pathogen leading to pyomyositis in patients with hematologic malignancies. A study at our institution demonstrated that *E. coli* pyomyositis was usually caused by members of the *E. coli* ST131 strain family. Researchers recently identified this group of strains in cases of fluoroquinolone-resistant, extended-spectrum, β-lactamase–positive *E. coli* infection worldwide. Authors have also reported cases of mycobacterial pyomyositis. Pyomyositis can be polymicrobial, especially in diabetic patients.

Pyomyositis develops in three stages: the invasive stage, which is accompanied by cramping muscle pain; the suppurative stage, which is characterized by severe pain and abscess formation; and the systemic toxicity stage, in which the affected muscle is fluctuant. Complications of *S. aureus* bacteremia can occur in patients with pyomyositis, leading to septic shock, endocarditis, septic emboli, pneumonia, pericarditis, septic arthritis, brain abscesses, and acute renal failure. Because bacteremia usually precedes the development of pyomyositis, all patients with bacteremia should be evaluated for organ involvement, including endocarditis, regardless of the stage at presentation.

Diagnosis, Treatment, and Prognosis

Identifying the causative organism is imperative for optimizing therapy for pyomyositis. Cultures of purulent material should be obtained after image-guided drainage or an open surgical procedure. A gram stain of the material should be performed.

Furthermore, other microbiologic stains are important when infections with fungal, parasitic, or atypical mycobacterial agents are suspected. Levels of muscle enzymes such as creatinine kinase and aldolase are paradoxically normal despite the presence of muscle inflammation.

Diagnosis of pyomyositis relies on imaging. A regular X-ray may show soft tissue swelling, and a computed tomography scan can show focal abscess formation as a low-density area with central fluid collection and a surrounding rim of enhancement. Magnetic resonance imaging shows a hypointense central area within the muscle with an enhanced rim. Magnetic resonance imaging is the test of choice because of its high precision and specificity.

When a distinct collection of pus is not present during its first stage, pyomyositis can be treated with antibiotics alone. Management of stage 2 or 3 pyomyositis involves surgical drainage with either computed tomography or ultrasound guidance or via an open procedure. These procedures should be performed urgently and ensure complete drainage of the purulent material. Broad-spectrum antibiotics covering *S. aureus*, especially methicillin-resistant *S. aureus*, as well as gram-negative and anaerobic pathogens should be administered intravenously. Antibiotic use should be modified on the basis of culture and sensitivity results.

The prognosis varies depending on the stage at which pyomyositis is diagnosed. In nonimmunocompromised patients, recovery is usually expected. In patients with malignancies, the prognosis is also dependent on the patient's underlying condition.

Paraneoplastic Myopathies

Polymyositis and dermatomyositis are the most common inflammatory paraneoplastic myopathies, and they can manifest with a broad range of extramuscular symptoms. Patients can present with typical skin lesions (Raynaud phenomenon). In contrast with patients with primary autoimmune myopathies, interstitial lung disease is rarely seen in those with paraneoplastic myopathies. Numerous epidemiologic studies have demonstrated the association between malignancy and inflammatory myopathies, with reported incidence rates of malignancies in patients with these myopathies ranging from 7 to 30 %. The temporal relationship between these two conditions can vary clinically. Malignancy can be detected before, at the time of, or after diagnosis of myositis, and an increased risk of cancer persists for 3 years after the diagnosis of myositis. Authors have reported many cancer types in patients with myositis, including breast, ovarian, lung, pancreatic, gastric, and colorectal cancers and lymphoproliferative malignancies. The association of dermatomyositis with cancer is reportedly stronger than that of polymyositis with cancer. A consensus regarding whether and how often patients with dermatomyositis or polymyositis should be screened for cancer is lacking. Most investigators recommend age-appropriate cancer screening with attention to risk factors related to the age and sex of each patient.

Pathogenesis of Inflammatory Myositis Associated with Cancer

The molecular mechanism underlying the relationship between cancer and inflammatory myopathies remains largely unknown. Histopathologic studies have demonstrated that cancer and autoimmune myositis share early signs of myopathy, with internally nucleated and regenerating myofibers and increased expression of neural cell adhesion molecules. In addition, regenerating myoblasts overexpress myositis-specific autoantigens. Researchers have observed similar myositis-specific autoantigen expression in several solid tumors of breast, lung, and hepatocellular origin. The body's immune reactions may be directed against tumor cells cross-reacting with regenerating muscle cells, causing autoimmune myopathies in genetically predisposed individuals. Several autoantibodies have been associated with cancer-related myositis, including anti-p155, anti-p140, and anti-TIF1-γ antibodies. Other more common myositis autoantibodies do not appear to be associated with increased incidence of cancer; these antibodies include the anti-synthetase antibody against Jo-1 and the Mi-2 antibody associated with dermatomyositis.

Emergency Conditions Associated with Inflammatory Myositis

Polymyositis associated with breast cancer reportedly causes ventilation failure secondary to respiratory muscle weakness. Patients with this condition must receive ventilation support in addition to immunosuppressive agents. Also, cardiac involvement is well recognized as a clinically important manifestation of polymyositis and dermatomyositis, although its actual frequency remains uncertain. However, cardiovascular complications represent one of the most frequent causes of death in patients with myositis aside from cancer and lung involvement. Asymptomatic cardiovascular features can be seen in patients with inflammatory myositis; these features include isolated electrocardiographic changes, valve disease, coronary vasculitis, ischemic abnormalities, myocarditis, and heart failure. Chronic inflammation can lead to myocyte degeneration, tissue fibrosis, and vascular alterations, which may explain the cardiac injuries observed in patients with myositis. Authors have reported that some myositis-specific autoantigens are associated with cardiac involvement of myositis. Clinically, electrocardiography, echocardiography, and cardiac magnetic resonance imaging are used to diagnose and monitor myocardial inflammation in patients with dermatomyositis or polymyositis. Endomyocardial biopsy has confirmed the diagnosis in some patients.

Treatment and Prognosis

Paraneoplastic dermatomyositis and polymyositis often respond to chemotherapy for an underlying malignancy. Rapid progression of myositis symptoms may require additional immunosuppressive therapy, although this is not desirable during cancer

treatment. This therapy includes high doses of prednisone, specifically, 1 mg/kg daily with a maximal dose of 80 mg for 4–6 weeks. Pulse therapy with methylprednisolone at 1 g/day for 3 days may be used at the beginning of therapy in patients who are severely ill.

Doses of corticosteroids should be tapered slowly, with close follow-up examination of the patient's muscle enzyme levels and improvement in muscle strength and any changes in the patient's rash. Myositis may improve with successful treatment of the cancer and return with cancer relapse. Thus, careful follow-up is recommended. About 5 % of patients with myositis will never have elevated muscle enzyme levels despite experiencing proximal muscle weakness and myositis-positive electromyography or muscle biopsy. In such cases, frequent assessment of muscle strength as corticosteroids are tapered is essential.

An important point is that some patients with dermatomyositis, with or without underlying malignancies, will have the typical rash but may never have clinically evident myositis. This is called amyopathic dermatomyositis, which is often associated with a malignancy. Control of the rash in these patients usually requires use of systemic corticosteroids in addition to topical treatment. For myositis patients with confirmed endomyocardial involvement, immediate immunosuppression starting with intravenous administration of corticosteroids is often needed. Second-line therapies used in the general population, such as cyclophosphamide, methotrexate, and azathioprine, may not be compatible with the patient's cancer treatment. If so, intravenous administration of immunoglobulin in addition to glucocorticoids is an alternative for resistant cases.

Skeletal Complications of Cancer and Cancer Treatment

Cancer patients are at risk for adverse events involving bones. Metastasis of cancer to bone and primary bone tumors can compromise bone integrity. In addition, various treatments of cancer cause long-term skeletal disorders, particularly bone loss, osteomalacia, and avascular necrosis. Chemotherapy, glucocorticoids, hormonal agents, and recently developed targeted therapies can affect bones in several ways. With the improved effectiveness of cancer treatments, more cancer patients are surviving and are doing so for longer periods of time. However, cancer survivors may experience fractures as long-term complications of bone loss, which is associated with decreased functional level and increased mortality rates.

Primary and Metastatic Musculoskeletal Tumors

Primary malignant bone tumors are relatively uncommon, with the highest incidences found in children and adolescents. Primary malignant bone tumors include osteosarcoma, chondrosarcoma, giant cell tumors, and fibrosarcoma. Another

malignancy affecting bone is multiple myeloma, most often in elderly individuals. Most bone lesions are metastatic malignancies, and the most commonly affected sites are the spine and pelvis followed by the long bones. As described previously, arthritis associated with metastatic carcinoma is often monoarticular and frequently affects the knee. Bone metastases are from breast and lung carcinomas in most cases. Primary and metastatic malignant bone lesions can be osteolytic or osteoblastic. Bone tumors can be diagnosed using magnetic resonance imaging. The most common symptoms of bone metastasis are pain, pathologic fractures, and neurologic deficits caused by the mass effect or fracture. The pain is usually a constant stabbing or dull ache that is worse at night and while bearing weight. Bone lesions may require surgical and radiologic intervention. Glucocorticoid use and emergency surgery are required for acute neurologic complications.

Osteoporosis and Osteoporotic Fractures

Bone is a metabolic tissue that undergoes a continuous remodeling process initiated by osteoclast-mediated bone resorption followed by osteoblast-driven bone formation. This dynamic process is tightly regulated by hormones, cytokines, and growth factors that influence not only osteoblast and osteoclast lineages but also the bone marrow microenvironment. Over the past 2 decades, the prevalence of osteoporosis and osteoporotic fractures in patients with cancer has increased markedly. Hormonal treatment, stem cell transplantation, chemotherapy, glucocorticoids, and radiation therapy can lead to bone loss via several pathways, including induced hypogonadism, direct bone toxicity, and renal tubular dysfunction.

Osteoporotic Fractures

Acute osteoporotic vertebral compression fractures can be crippling. These fractures are associated with severe back pain, immobility, physical decline, and a potential for increased risk of death. Many patients with cancer who experience osteoporotic fractures are elderly and have undergone chemoradiation that further damaged their bones. Researchers have observed high incidences of osteoporotic fractures in patients who survived breast cancer, prostate cancer, or lymphoma.

Bed rest, analgesia, and external bracing are conventional treatments of osteoporotic fractures, with varying success. According to the natural courses of vertebral fractures following treatment using conservative measures only, most patients become pain-free 6 months after fracture occurs. However, a large number of patients sustain incapacitating pain at the end of 12 months. Predictors of early pain relief or the transition from acute to chronic pain have yet to be identified.

Percutaneous vertebroplasty (PV) is an alternative treatment of acute osteoporotic vertebral compression fractures that are refractory to conventional therapy. However, the efficacy of PV has been a topic of debate recently. Discrepancies in

efficacy among studies of PV are probably related to varying criteria for patient selection. In studies in which the patient population included those with chronic pain (up to a year after the fracture) and those with low to intermediate levels of pain, the efficacy of PV did not differ from that of conventional measures. However, in several new studies in which only patients with severe pain who had fractures within the previous 6 weeks were enrolled, both PV and conservative therapy reduced their pain, but patients in the PV group had markedly better physical functioning, less need for medication, and lower visual analog pain scores than did patients in the conventional treatment group at 1 and 4 weeks after treatment. Although pain scores at 12 months after initiation of treatment were similar in the 2 groups, pain medication requirements were lower in the PV group at all 3 time points.

Some researchers have expressed concerns that PV may increase the risk of new vertebral compression fractures in adjacent vertebrae. A recent study demonstrated that PV itself is not associated with an increased risk of new fractures. However, the number of vertebral fractures at baseline is predictive of the risk of future fractures. Therefore, PV may be considered for selected patients who have acute vertebral fractures for up to 6 weeks, whose fractures have not responded to pain medications, and who have remained bed-bound and dependent on narcotics. In such cases, PV may produce prompt pain relief and mobilization and prevent further complications.

Avascular Necrosis

Avascular necrosis of bone results from compromised bone vasculature, leading to death of bone and marrow cells and, ultimately, mechanical failure. In the general population, glucocorticoid use and excessive alcohol intake account for more than 90 % of avascular necrosis cases. Avascular necrosis is reported to be a complication of chemotherapy, high-dose glucocorticoid use, and radiation therapy in patients with cancer. Investigators have observed that up to 1 % of patients with acute lymphoblastic leukemia experienced avascular necrosis within 3 years after undergoing chemotherapy and that the incidence rate was even higher in patients who underwent chemotherapy that included very high doses of glucocorticoids.

Radiation therapy also may induce osteonecrosis. Radiation-induced osteonecrosis of the jaw is a severe complication of radiation therapy for head and neck cancer, most often when it involves the mandible. Radiation-induced osteonecrosis can range from small, stable, self-limited, asymptomatic bone exposure to severe necrosis requiring surgical intervention and reconstruction. Clinically, patients with osteonecrosis of the jaw may present with pain, bad breath, dysesthesia, trismus, mastication difficulty, fistula formation, pathologic fractures, and/or recurrent local or systemic infection. Irradiation of the pelvis can lead to pelvic insufficiency fractures. Failure to diagnose osteonecrosis and insufficiency fractures may lead to additional irradiation, delayed treatment, and prolonged morbidity.

Among patients who have undergone stem cell transplantation, researchers have observed increased rates of osteonecrosis in those with low bone density at the femoral neck. Whether low bone mass is an independent risk factor for osteonecrosis in these patients is unclear. Treatments of osteonecrosis include minimizing the inciting

event, conservative measures that allow the bones to bear partial weight, and limited debridement. Surgical intervention with core decompression has been useful in relieving pain in selected patients with osteonecrosis involving the hip and shoulder. In one uncontrolled study, alendronate (10 mg/day) was administered to 294 patients with osteonecrosis of the hip to determine whether use of bisphosphonates to slow resorption of necrotic bone is beneficial. Treatment with alendronate decreased pain and delayed the progression of femoral head collapse to levels lower than those produced by conservative treatment according to historic data for the latter treatment.

Bisphosphonates are increasingly used to treat both metabolic and metastatic bone diseases. Intravenous bisphosphonates are most frequently administered as part of chemotherapy for tumors in bone, such as multiple myeloma and metastases from breast, prostate, and lung cancer. A retrospective study at our institution demonstrated that osteonecrosis of the jaw is an uncommon but long-lasting disorder that occurs mainly in patients with breast cancer or multiple myeloma treated with intravenous bisphosphonates. High cumulative doses of bisphosphonates, poor oral health, and dental extractions may be significant risk factors for osteonecrosis of the jaw. Osteonecrosis resolved in 23 % of the patients in this study after conservative therapy. In 40 patients for whom conservative therapy failed, antibiotic therapy and surgical debridement of all necrotic bone along with tension-free primary closure led to uneventful healing without further bone breakdown.

Vasculitis and Vasculitides

Paraneoplastic vasculitides represent approximately 2–5 % of all vasculitides. They are more often associated with lymphoproliferative disorders and myelodysplastic syndrome (1 in 1800 cases) than with solid tumors (1 in 80,800 cases).

Paraneoplastic Vasculitides

Paraneoplastic vasculitis is often characterized by inflammation of small- or medium-sized blood vessels. The most common form is leukocytoclastic vasculitis, a small-vessel disease characterized by the appearance of palpable purpura. Infrequently, medium-sized-vessel vasculitis mimicking polyarteritis nodosa develops in association with hairy cell leukemia. Systemic vasculitis is associated with malignancy much less often than is leukocytoclastic vasculitis. Also, authors have reported vasculitis of the intestine but at a much lower frequency. Vasculitis associated with a hematologic malignancy frequently precedes the diagnosis of the malignancy, but it may occur after the diagnosis or during malignancy recurrence. In patients with malignancies, proposed mechanisms causing vasculitis include deposition of immunocomplexes of tumoral antigens and antibodies, cross-reaction of antibodies directed against antigens on leukemic cells with endothelial cell walls, and direct damage to the vascular wall by leukemic cells.

Paraneoplastic vasculitis often responds poorly to conventional therapy for vasculitis. Initially, treatment with corticosteroids may result in improvement or resolution of the vasculitis, but relapses are common, and the addition of cyclophosphamide is usually necessary, especially in patients who present with polyarteritis-like symptoms. Chemotherapy directed against the underlying malignancy reportedly lessens the severity of vasculitis but generally is only partially effective. Prognosis is dependent on the type and stage of the primary malignancy.

Raynaud Phenomenon and Digital Ischemia

Raynaud phenomenon is characterized by episodes of pallor, cyanosis, and erythema with sharp demarcation in the distal portions of the fingers and toes as a vascular response to cold temperature or emotional stress. Symptoms result from low blood flow or ischemia. In mild cases, skin changes, numbness, and the "pins and needles" sensation are completely reversible after rewarming of the skin. In severe cases, pain, digital ulceration, and necrosis may occur; these are thought to be secondary to vasoconstriction of digital arteries and cutaneous arterioles. When cyanotic discoloration does not resolve, it may be a sign of irreversible ischemia, constituting an emergency. Raynaud phenomenon is considered to be a primary condition when no underlying vascular or connective tissue disease is identified; this can occur in 3–5 % of the general population. Patients can be predisposed to secondary Raynaud phenomenon because of pre-existing occlusive vascular disease, connective tissue disease, malignancy, or drug use. Paraneoplastic Raynaud phenomenon, which is relatively rare, is associated with carcinomas, sarcomas, lymphomas, and leukemia. Cancer patients undergoing chemotherapy with drugs such as bleomycin, cisplatin, and vinblastine can be at higher risk for Raynaud phenomenon than patients undergoing other therapies.

Use of interferon-α, which is administered to patients with high-risk melanoma, is reported to be associated with Raynaud phenomenon. The symptoms and signs of the phenomenon are often limited to a few digits, but in severe cases, the hands and feet are affected, leading to frank necrosis of digits. In patients with mild attacks of Raynaud phenomenon, therapy can be continued without aggravation of symptoms. In severe cases, interferon-α use is discontinued. Treatment with calcium channel blockers can sometimes alleviate the symptoms. Continuous intravenous infusion of prostaglandins should be initiated in patients with pending necrosis to avoid amputation.

Emergency Conditions Associated with Other Co-existing Connective Tissue Diseases

Cancer patients with pre-existing rheumatologic conditions can sometimes present with emergent conditions. These can occur as part of a disease process or as complications of cancer treatment. In addition to septic arthritis, an important joint

emergency is atlantoaxial dislocation secondary to overextension of the neck during intubation for surgery in patients with rheumatoid arthritis. Other emergencies are related to systemic connective tissue diseases, which can result in respiratory failure, renal crises, and cerebrovascular and cardiac emergencies. A patient with polyarteritis nodosa may present with gastrointestinal bleeding, intestinal perforation, or acute pancreatitis. Respiratory emergencies can manifest as adult respiratory distress syndrome, pneumonitis and diffuse alveolar hemorrhage caused by lupus or systemic vasculitis, or respiratory failure owing to muscle weakness because of polymyositis and/or dermatomyositis. A renal crisis can be precipitated by the systemic use of intermediate to high doses of glucocorticoids in scleroderma patients. Unrecognized vasculitides such as microscopic polyangiitis and Wegener granulomatosis can cause renal failure. Cerebrovascular events, cortical vein thrombosis, and acute psychosis can be neurologic complications of lupus. Cardiac emergencies include tamponade, acute myocarditis, and acute myocardial infarction caused by a lupus or myositis flare-up. Acute vision loss can occur in patients with temporal arteritis, Behçet syndrome, or seronegative spondyloarthritis. Catastrophic antiphospholipid syndrome is an emergency condition that can affect multiple organs.

Management of these emergencies includes immunosuppression, intensive care, and withdrawal of the potential inciting drug. Anticoagulants must be used in addition to immunosuppressants in the management of antiphospholipid syndrome.

Conclusion

The ability to recognize signs and symptoms of rheumatologic and orthopedic emergencies along with a good understanding of patients' underlying conditions is of paramount importance for early identification and proper management of these emergencies. The assessment of and management for a cancer patient with a rheumatologic emergency requires careful diagnosis to determine whether the condition is secondary to the cancer, either from invasion of adjacent structures or as a paraneoplastic syndrome; caused by an infection; an adverse event arising from therapy; or a primary rheumatologic condition. Prompt therapy must be implemented to ensure adequate control of comorbidities and allow for continuation of cancer therapy.

Key Practice Points

- Monoarthritis is the condition that most frequently necessitates urgent rheumatologic consultation in a cancer center. Septic arthritis should be suspected, and arthrocentesis should be performed immediately. Treatment with empiric antibiotics should be administered to prevent permanent loss of function until symptoms resolve.
- Acute crystal-induced arthritis frequently occurs in patients with cancer. A sudden change in uric acid production owing to cancer treatment can cause acute gouty

arthritis, and dehydration and immobilization can precipitate flare-ups of gout and CPPD disease.

- Malignancy-associated inflammatory myositis can resolve with successful treatment of the underlying cancer. Cancer recurrence should be suspected in a patient with a history of cancer in whom inflammatory myositis develops.
- Vasculopathy and Raynaud phenomenon are associated with a variety of malignancies; treatment should be directed at the underlying malignancy as well as these symptoms.
- Painful pathologic fractures can occur in bones in which primary or metastatic tumors are involved that can lead to neurologic deficits. Surgery and other therapeutic modalities can decrease the pain and preserve function.
- Osteoporosis induced by cancer or its treatment is common. Acute pain associated with vertebral fractures that do not respond to conservative treatment may be treated with percutaneous vertebroplasty.
- Patients with pre-existing rheumatologic diseases may present with acute flare-ups during cancer treatment, which must be addressed promptly to avoid disruption of cancer therapy.

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Chapter 8
Cancer Care Ethics in the Emergency Center

Colleen M. Gallagher, Jessica A. Moore, and Jeffrey S. Farroni

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Chapter Overview

The emergency center (EC) is a technical, specialized, fast-paced environment where time is of the essence. Falling into a process by which the need for immediate response overshadows the need for ethical examination of important aspects of

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patient care is easy. Our purpose is to provide clinicians with some ethical considerations that can be made and reduce challenges to caring for the cancer patient in the EC. Cancer patients are often seen in ECs because of issues at the end of life, uncontrolled physical pain, and psychosocial or coping issues. This chapter deals with some of these and other common issues, including delirium, quickly changing conditions, and possible drug-seeking behaviors for coping. Also considered are clinician responses to these as well as issues to recognize when assisting patients and their surrogates with decision-making during these difficult times. Case examples, discussion of the ethical challenges, and suggestions for the clinician and health care team are used to highlight and examine some of the ethical dilemmas faced in the EC.

Introduction

Cancer patients in ECs may pose special challenges because of the nature of their disease processes, pain control, and their increased incidence of end-of-life issues. Emergency physicians practice in an institutional setting, usually the EC of a hospital, and must work closely with prehospital providers, hospital consultants, and outside physicians. Decisions regarding treatment and disposition are often influenced by institutional policies and practices. The ethical values steeped in clinical decision-making represent an inescapable element of patient care in the emergency center. These values include autonomy, informed consent, and decision-making capacity, which are concepts that are foundational to Western bioethics.

Respect for an individual's political and legal right to self-governance (autonomy) is dependent on the individual's ability to make decisions based on the information disclosed and weighed against his or her values and preferences (decision-making capacity) and, thus, ability to give permission for the proposed action (informed consent). Patient autonomy refers to the right of the patient to participate in the decision-making process and direct the course of his or her medical treatment within the bounds of medically and ethically appropriate options. If a patient does not have decision-making capacity, the physician should seek the permission of the appropriate surrogate decision-maker for treatment and inform him or her before treatment in the same manner that would be used with the patient if the situation allowed it.

We present below several case examples to illustrate common ethical challenges with cancer patients in ECs and the ethical principles used to deal with them. Highlighted at the conclusion of this chapter are practice points to assist clinicians when faced with cases involving questions of autonomy (patient and provider), informed consent for medical treatment, decision-making capacity, surrogate decision-making, advanced care planning and advance directive documents, personal and professional culture and values, withholding and withdrawing treatment (including life-sustaining measures), beneficence and nonmaleficence, justice, and professional integrity.

Informed Consent and Treatment Refusal

Case

A 62-year-old woman with breast cancer who has been receiving adjuvant chemotherapy and has resultant myelosuppression presents to the EC after an episode of melena. She feels weak and dizzy, but she is hemodynamically stable. She is thrombocytopenic, with a platelet count of 12,000/μL, and anemic, with a hemoglobin level of 6.1 gm/dL. The patient appears to be confused when giving information about her chemotherapy, specifically, the dates and number of cycles she has received. The emergency physician advises her that she may need transfusion support, but she declines, stating that her personal beliefs do not allow her to accept blood products.

Ethical Challenges and Principals

As a clinician, you are faced with the choice of whether to accept the patient's refusal. An important point to keep in mind is that informed consent is a process. Consent must be given or refused with full knowledge of the benefits, risks, and burdens of what is being offered and the alternatives to the proposed therapy. Sufficient information must be provided to the patient or his or her legal representative, usually a medical power of attorney or guardian.

Ethicists would likely ask you several questions. Have you presented the patient with enough information? Have you presented any treatment alternatives, if any exist? Have you determined whether her confusion is sufficient to warrant an assessment of her decision-making capacity? Have her beliefs been verified, such as with a previous statement or declaration of faith tradition known for that belief? All of these factors are related to the patient's ability to make autonomous decisions.

In a situation like this, the patient does not accept an aspect of the practice of medicine. This may be in direct opposition to what is available and the standard of care in the medical community.

Culture can play a large role in how patients make medical decisions. Because culture is a combination of attitude, behavior, words, beliefs, perceptions, and values, we must take the time to understand them for our patients when dealing with their decision-making. Thinking that all people who state a belief about transfusion of blood or blood products believe the same thing or are in the same faith community can be dangerous. Obtaining information from this patient about her belief is important. She may be a Jehovah's Witness, or her belief may be based on familial experience in which someone received blood and his or her situation did not turn out well.

To understand a patient's values in making a decision, the clinician must be culturally competent, have the desire to inquire and learn, and adapt his or her presentation. This will provide the necessary information about the patient based on the new knowledge that is acquired.

Patients can refuse offered treatments and interventions even in emergencies. Often, the challenge for the emergency physician is knowing how to deal with a refusal. This is especially true when a patient expresses a cultural or faith system that diverges from the clinician's. When the clinician attempts to give information to a patient with some understanding of his or her values, accepting the patient's refusal and remaining compassionate while addressing any symptoms that can be managed under the limitations placed by the patient may be necessary.

Cancer Patient with Acute Pain

Case

A 34-year-old patient presents to the emergency room complaining of severe hip pain. A review of her history indicates she was diagnosed with a femoral neck chondrosarcoma 2 years ago. At that time, she underwent a resection of the femoral head and neck and had a left hip hemiarthroplasty followed by conversion to a total hip arthroplasty. She has been experiencing chronic pain since her diagnosis. She rates her current pain as a 9 on a verbal pain scale (0–10).

The patient's hip pain has been assessed by her primary physician, and she has been taking a regimen of transdermal fentanyl (25 μg) supplemented with morphine (immediate release; 15 mg 3 times a day) to attain a satisfactory level of pain control. During her last visit 2 weeks ago, the patient's drug screen was positive for opiates and cocaine. She was informed that her prescriptions would not be renewed owing to the presence of oxycodone in her screen. The staff informed her that providing scheduled analgesics for any patient who tested positive for a suspected drug of abuse was against their local policy. She was instructed to return in a week and that she could be given pain medication if she demonstrated discontinued use of cocaine.

The patient states that earlier in the day, she went to see her pain management team and was informed they would not dispense pain medication because she had another positive urinary drug screen, this time for amphetamines. According to the nurse practitioner present at the visit, the patient became extremely upset and agitated and verbalized having thoughts about shooting herself. The patient left the office and went to the EC several hours later. The patient claims that she currently does not have any suicidal thoughts and has no intent to harm herself. She also denies ever having tried to harm herself. She does admit to having difficulty controlling her mood and having "racing" thoughts that make sleep difficult. Moreover, the patient has been hospitalized for insomnia. She admitted that she occasionally uses marijuana to ease both her pain and her insomnia. She has a psychiatric diagnosis of bipolar disorder, ongoing medical management of which includes quetiapine hemifumarate (Seroquel), paroxetine hydrochloride hemihydrate (Paxil), valproic acid sodium salt (Depakote), clonazepam (Klonopin), and hydroxyzine dihydrochloride (Atarax). The patient denies abusing any other drugs or alcohol.

Ethical Challenges and Principles

Pain is a common reason for seeking medical attention at an EC. Emergency providers have an ethical duty to alleviate pain, particularly because they "have been given a unique social role and responsibility to act as health care providers of last resort for many patients who have no other feasible access to care." Despite the pressures of working in a stressful environment, emergency physicians must "prevent or minimize pain and suffering, loss of function, and loss of life." In general, pain management is well known to often be inadequate. Cancer pain in particular is highly prevalent and a great source of suffering and despair. Patients with cancer may present to the EC looking for relief from acute pain. Complicated medical histories are not uncommon among cancer patients, and understanding their pain sequelae in the context of their disease is particularly important.

Health care providers often express concern regarding the chronic use and potential for abuse of opioid analgesics. Their concerns are exacerbated with evidence of forum shopping by a patient for pain medications, a history of drug abuse, and positive screens for controlled substances used for self-medication. An ethical approach in caring for a cancer patient includes the imperative to address pain. Treating pain in this context includes understanding both the physiologic causes and its psychosocial and contextual features.

This patient's history makes evident that she has been diagnosed with and given treatment of chondrosarcoma. The primary question is how should the attending physician treat this patient's pain, particularly if he or she is concerned about psychiatric issues and the potential for analgesic abuse? A conflict arises between the duty of care to decrease the patient's pain and the obligation not to be an instrument of addictive and destructive behaviors. Beyond being complicit in such behaviors, a physician may worry about squandering precious resources on nonadhering patients and the larger societal costs attributed to drug addiction. This case presents several ethical dilemmas, including determination of when the risk of drug abuse outweighs the benefit of pain relief and whether this risk ever outweighs the benefit when pain is cancer-related. The ethical principles to be considered in such cases are beneficence, nonmaleficence, risks versus benefits, resource allocation and justice, and professional integrity.

The primary concern should be the patient's complaint of pain. Discerning the etiology of the pain is important, particularly if it is related to cancer progression, treatment, and/or symptom burden. The mere suspicion of opioid misuse should not serve as a justification for discrediting or marginalizing the patient's experience of pain. In the present case, the patient had a positive screen for a pain medication that was not prescribed for her. The strict adherence of the clinical team to its hospital's policy regarding prescription of analgesics to patients with positive drug screens immediately frustrated the patient. The policy is sound in that it attempts to mitigate the acquisition of drugs by individuals who may abuse them. However, the clinical team's "take it or leave it" approach apparently did not serve the patient's best interests. Deeper questions must be asked to better understand the apparently dire need

Table 8.1 Selected core principles of safe, effective pain management

1.	The patient's *self-report of pain* is a *critical* component of a comprehensive pain assessment.
2.	Optimal pain treatment may be enhanced by *acknowledging cultural differences* in the expression of pain.
3.	A *comprehensive assessment*, including the patient's self-report of pain, will enable the clinician to better evaluate the patient's experience.
4.	Analgesic-based management of pain should *begin as soon as possible* when indicated. Diagnosis of the pain etiology should not delay administration of analgesics.
5.	Providers must *consider the special needs of patients with addictive disease* to ensure adequate, safe delivery of analgesia.
6.	Individuals who appear to present with behaviors suggestive of addictive disease should be given brief interventions and referrals for substance abuse treatment. Chronic repeat visits to non-continuity-of-care providers can be addressed via social service interventions, care plans in conjunction with primary care physicians, and *analgesic contracts for emergency pain relief*.
7.	At the end of a health care visit, the patient should receive instructions with an *individualized pain treatment plan*, including important medication-specific safety considerations.

of the patient for pain medication. Is this really drug-seeking behavior? Does the patient have an underlying psychologic issue at the root of her behavior? Is the patient's cancer-related pain not being managed well? A claim that her pain is not being managed would not be audacious, as a substantial body of literature has documented inadequate pain control, even in emergency settings.

The physician should also look for other information in understanding the patient's life, such as the home living environment, support system, and life concerns other than cancer. This will inform other needs that may be addressed by the interdisciplinary team in hopes of positively impacting the patient's care. The physician should assess the patient's perspective on his or her quality of life and therapeutic expectations and gauge how well those expectations are realistically grounded. Discerning what the patient really wants is important. Is it solely pain management, or is it the underlying concerns related to the cancer, medical issues, or other personal matters in developing a comprehensive approach to the patient's care? Table 8.1 lists a selection of principles that may be used to guide pain management.

Although this patient denied having suicidal ideation, the report of the nurse practitioner should be taken seriously. An entirely reasonable possibility is that the patient was merely venting frustration about the hospital's policy and her desire for relief. On the other hand, her comments should not be overlooked, as a psychiatric consult or follow-up visit to the patient's mental health provider may be necessary. The patient's history also may provide insight into treatment adherence. What are the patient's obligations? Patients and caregivers obviously have important roles to play in adhering to treatment plans. Patients also have ethical obligations during the course of their treatment, including consideration of the medical team's advice, compliance, and adherence to a medical contract, if necessary. This contract is commonly employed in situations with concerns about opioid-based therapy and used to formalize an agreement between the physician and the patient. In the present case, should the physician have a concern that the patient may abuse an appropriately prescribed analgesic, an agreement may be used to dispense just enough medication

Table 8.2 Pain management in cancer patients suspected of substance abuse

1. Define the mechanism of the pain and treat the primary problem (i.e., infection, tissue ischemia).[a]
2. Distinguish the temporal characteristics of the abuse behavior.[b]
3. Follow relevant pharmacologic principles of opioid use.[c]
4. Nonopioid therapies should be given concomitantly with or even in place of opioids.
5. Specific drug abuse behaviors should be recognized and dealt with firmly.
6. Caregivers should set limits to avoid excessive negotiation about drug selections or choices.

[a]Attention to the primary causes of pain symptoms may greatly reduce the requirement for and negotiations about opioid analgesics

[b]The implications are different for a patient with a recent history of active drug abuse who may need higher than usual starting doses of opioids and one who may not be able to set limits on drug use

[c]Treatment with an opioid agonist-antagonist should not be started for a patient who is tolerant to opioid agonists such as methadone. Mixed agonist-antagonists may precipitate withdrawal if given in this setting

to treat the patient's immediate needs until she can follow up with her regular provider. Table 8.2 provides an approach to managing pain in cancer patients for whom substance abuse is suspected.

Case Continued: The Patient Returns

Case

Assume the 34-year-old cancer patient described above is prescribed fentanyl and morphine for 2 weeks with instructions to follow up with her primary physician. The patient presents to the EC again 4 days later having used the entire 2-week supply of her pain medications and requesting a refill. What should the emergency physician do? Also, what should be done if imaging of the patient reveals a suspicious lesion, and she is to undergo biopsy in 3 days followed by either surgical replacement of the femur or revision arthroplasty? Would this finding alter the course of action?

Ethical Challenges and Principles

When the patient returns to the EC, physicians find evidence that she has used her medication much more quickly than indicated. Furthermore, she now has even more evidence of substance abuse. Patients may engage in this revolving door of emergency care needs and drug-seeking behavior, which poses challenges to the medical team described above. A common issue is whether the patient can be discharged from care owing to noncompliance. A physician has a professional, not to mention legal, duty to

keep from being complicit in illegal activities. At the same time, the patient may be in legitimate distress, pain, and suffering. Because emergency physicians want to engage in informed decision-making, they must consider the importance of the patient's ability to understand his or her treatment options. This requires the physician to carefully explain not only the decisions being made but also the rationale for those decisions. For example, if a physician decides not to prescribe opioids, providing a sound rationale for not doing so as well as alternatives to treatment of pain will make that decision appear to be beneficial rather than punitive to the patient.

Does the approach change with the added information that the patient has a new lesion? This may make the physician sympathetic to the possibility that the return of her cancer is a legitimate cause of pain. Thus, the physician may be inclined to work with the patient. At the heart of the matter, a physician should take a compassionate approach to pain management that includes strategies for providing the best method of alleviating a patient's cancer pain.

Pain, Delirium, and Surrogate Decision-Making

Case

A 51-year-old man has been brought to the EC by paramedics. They were called by his 25-year-old daughter, who was visiting from out of town. The patient previously left the hospital after several months of treatment of pancreatic cancer failed to stop or even slow the progression of the disease. When he was told that his disease had metastasized to the liver and doctors gave him no further aggressive treatment options, the patient chose to enter the care of a home hospice service. That was 27 days ago.

The paramedics were called because the patient was waving his hands and speaking of seeing angels and people from his past who had died. He seemed confused about night and day. He also could not remember his children, confusing them with his own brother and sister. He said he had no pain, but he moaned often.

The patient's wife and 19-year-old son are his primary caregivers, but they were away for the afternoon. His daughter and her husband and child, who live about 200 miles away, were caring for him at the time. The patient's mother also came to the EC. It was she who called the paramedics and was telling the staff, "My son will not die today and will not die in pain!"

Ethical Challenges and Principles

Delirium is the most common neuropsychiatric syndrome in patients with advanced cancer, particularly elderly patients. It is associated with a high degree of distress in patients, families, and nurses. Delirium is reported at rates ranging from 8 % to 17 % in elderly patients seen in general ECs. Missing a diagnosis of delirium may

cause treatment errors, as delirious patients are often given medications to control pain that is not actually present.

The ethical concerns in this case may center on following the patient's autonomous decisions or accepting a demand to override them by following the wishes of a surrogate decision-maker. The patient's decision was to recognize and accept that his life is nearing the end and undergo hospice care. He is now presenting with possible pain or delirium, which hospice clinicians have the ability to treat.

The primary concern is treatment of the patient's symptoms. This means assessment of him for pain and delirium and then treating what is found. This is based on "doing good" and "avoiding harm" for the patient. Some of his family members have a different opinion. In this situation, documentation from an advance directive by the patient as to whom he would like to make decisions for him when he is unable to do so is missing. He has a wife who is not available in person or by telephone at this time. He also has a daughter who is present and a mother who is both present and demanding treatment of his pain and admission of him to the hospital. The physician must determine whether to follow the decisions of the available surrogate decision-makers, wait for his wife to be available, or adhere to the patient's previous decision to use hospice services.

A surrogate decision-maker can be the best option when a patient cannot directly give his or her decision about emergency care. The hope is that the surrogate will know the patient and which decision the patient would make. An advance directive, in which the patient assigns an individual as a surrogate and gives guidance regarding such decisions, is usually very welcome in such circumstances. Written advance directives are not always available, however. When in doubt about the identity of the appropriate surrogate, check with the hospital's risk manager.

In the present case, the patient made one choice, and at least one of his possible surrogate decision-makers is demanding something different. Thus, the ethical dilemma is related to autonomy and surrogate decision-making. The demand by the patient's mother for pain medication and inpatient admission is a barrier to, or at least a distraction in, the patient's treatment. Individuals may make any such demands or requests based on a lack of information or on personal fear. This case demonstrates that informed consent is essential for appropriate treatment under such scenarios. This can only happen with proper assessment of symptoms and the disease process so that the important information shared is accurate and timely. No matter who the surrogate decision-maker may be in a given situation, following a good informed consent process is essential.

Resuscitation

Case

A 25-year-old Jewish woman who is married and the mother of a 2-year-old has a history of depression that is being treated but is otherwise healthy. In December, she began experiencing left knee pain. In February, she had an open biopsy of a mass on

the knee that had developed since December. She was diagnosed with a high-grade osteosarcoma of the proximal left tibia at an outside hospital. She presented to the cancer center the following month and was evaluated by orthopedic and sarcoma medical oncology specialists. With knowledge of an expected cure rate of 70 %, she began undergoing chemotherapy soon after. After several rounds, her therapy was adjusted owing to neutropenia, thrombocytopenia, and severe mucositis. Two months into treatment, she was evaluated using computed tomography angiography, which yielded a small right common ileac vessel aneurysm versus thrombosis. She began receiving anticoagulation therapy with enoxaparin sodium (Lovenox). One week later, the patient was transported to the EC on active cardiopulmonary resuscitation (CPR), which was started 1 h before arrival at the EC. The patient arrived intubated and had received atropine, epinephrine, and several shocks.

Information about the patient was obtained from a friend who witnessed her collapsing after flushing her central venous catheter line with heparin. Her friend did not notice any concerning symptoms like fever, vomiting, diarrhea, shortness of breath, or bleeding before the collapse. Initially, CPR yielded no palpable pulse or blood pressure, unresponsive dilated pupils, ventilation of both lung fields, and no heart rate. Cardiac monitoring revealed electrical activity alternating with asystole, resulting in pulseless electrical activity. CPR was continued in the EC for 1 h and 40 min. The primary team was informed about the patient's condition. Colleagues in the intensive care unit and the chair of the CPR committee were consulted. Also, the cardiology service was consulted to evaluate the patient for cardiac tamponade. After a total of 2 h and 40 min, the patient had spontaneous agonal breathing, monitoring demonstrated a sinus rhythm of 98 beats per minute, her pulse was palpable, and her blood pressure was not obtainable. The code team was present and transported the patient to the intensive care unit.

The patient's husband was at their home in another state and kept informed of her condition via telephone. His constant request was to evaluate his wife's brain activity and remove life support if she was brain-dead. The EC physician contacted the neurology service to evaluate the patient for brain activity or death. In addition, the patient's father contacted the EC by telephone. However, the physician could not communicate with him, as the patient's father was not willing to listen while making his demands. His constant request was to continue all life-saving measures or he would sue the hospital.

Ethical Challenges and Principles

We will use this case to summarize many of the important aspects of ethical decision-making in the EC described earlier in this chapter. According to the doctrine of informed consent, physicians must first inform the patient with decision-making capacity about the nature of his or her medical condition and treatment alternatives and their expected consequences and then obtain the patient's voluntary consent to the treatment. As in many cases in the EC, the present patient was not in

a position to exercise autonomy and provide informed consent or refusal for the emergency treatment necessary to save her life. The goal of emergency medicine is to act quickly when caring for individuals with acute illnesses or injuries to prevent or minimize pain and suffering, loss of function, and loss of life. Often, initiation of treatment cannot be delayed to obtain informed consent from the patient or even the surrogate decision-maker. For patients with questionable or no decision-making capacity, and in the setting of immediate need for treatment, emergency physicians intervene to prevent death using the emergency exception rule, also referred to as presumed consent. This is invoked when clear instructions from surrogates, personal physicians, or written directives are not available. According to the principle of presumed consent, physicians act in life-threatening situations under the assumption that life should be preserved in the absence of clear wishes to the contrary by patients or proxies. Treatment that is provided based on presumed consent is founded on the principle of beneficence.

Most states provide instruction on who has the authority to make medical decisions in an incapacitated patient's stead. This dictated hierarchy of decision-makers usually starts with court-appointed guardians and individuals named as powers of attorney for making health care decisions then proceeds to various categories of adult next of kin. In the present case, the state of Texas dictates, as do most other jurisdictions, that if this patient has not named another individual in an advance directive document, her husband is the legally authorized decision-maker. Next would be any grown children followed by the patient's parents. In the case of a minor patient who is not married and therefore emancipated, the primary individuals with decision-making authority on behalf of the patient would be his or her parents or guardians. In the case presented herein, both the patient's husband and father were providing instructions regarding her treatment. We can assume that both were instructing the health care team to act in a manner that would benefit the patient and be consistent with her wishes based on her values, in other words, follow the principle of beneficence—to do good for or act for the benefit of another—a principle inherent in the medical profession and at the core of emergency medicine. The medical team was probably feeling unnecessary pressure to act in a manner that could cause harm, however. Even if the husband and father believed they were acting in the patient's best interests, their instructions may have been perceived as conflicting. When more than one interested party is involved in surrogate decision-making, consensus is ideal but may not be possible. In the present situation, the treating physician may not have been able to lead toward a consensus, especially over the telephone, but other members of the health care team may have been able to assist in discussions that would clarify the patient's current condition, elucidate the husband's and father's understanding of the situation and reasons for their instructions, and clarify misunderstandings. Good communication under such a scenario is always important, even when time is short.

Life-threatening situations afford little to no time for consultation with other physicians or surrogate decision-makers or seeking advance directives for health care that may provide more information regarding this patient's underlying condition and prognosis or her values and wishes regarding medical treatment. This scenario does

not tell us whether the patient completed and provided to the hospital advance directive documents that may have given guidance to the emergency care providers. The conversations with the patient's husband and father may have indicated her values and, more clearly, their own values. Furthermore, ascertaining how the patient's faith might have affected her wishes or the instructions from her family members may have been difficult because of the need for immediate action. As time passed or after she was transferred to the intensive care unit, the emergency team or intensive care team may have had an opportunity to explore this issue. Similar to the first case described in this chapter, a patient's faith and/or cultural tradition may have a significant effect on medical decisions. Medical ethics is built upon the intersection of historical understanding and practices of philosophy, theology, and science. Teachings based on evolving interpretations and advancing knowledge and technologies in these disciplines can lead to a spectrum of practice. When time allows, exploration of these factors may aid shared decision-making or elucidate the reasons behind peculiar or conflicting decisions. Culture and faith likewise can shape the values of emergency care providers, thereby affecting health care providers' decision-making processes and actions.

Faith and cultural traditions can influence specific medical interventions, such as initiating, withholding, or withdrawing life-sustaining measures. Decisions to withhold or withdraw life-sustaining treatments are often difficult to make in an emergency setting. This results from a lack of an ongoing long-term relationship with the patient and his or her family and of time to weigh the decision to limit life support based on medical circumstances. However, these decisions undeniably are an integrated part of medical activity. Physicians, including emergency physicians, are under no ethical obligation to provide or maintain treatments they judge to be of no benefit to patients, but making that judgment can be difficult in the first few moments of a life-threatening emergency. Once the patient has been stabilized, assessment of his or her medical condition, underlying disease, and cause of acute deterioration may lead to the determination that withdrawal of treatment is an appropriate option. In Western bioethics, withholding and withdrawing nonbeneficial treatments hold equal weight in the abstract because either of them, when appropriately applied, allows death to occur naturally owing to the underlying condition. In practice, however, they can feel very different. Some physicians may feel that withholding an intervention is more appropriate than withdrawing one in progress because withdrawal could be interpreted as participating in or hastening the patient's death. Others believe that a stronger argument exists for initiating treatment in an emergency situation and withdrawing it if appropriate when more information is available and can be weighed carefully.

Ethical dilemmas are borne out of conflicts of values and principles, the resolution of which reasonable people may disagree about. This may manifest in competing patient and physician autonomy; competing principles of autonomy versus beneficence, which ideally must be balanced; differing goals of care; or conflicting definitions of beneficence. Often, assessment of beneficial treatment yields different outcomes according to the medical team and patient or surrogate. This may result from different estimations of acceptable quality of life or definitions of benefit and

burden or harm. Quality of life and burden of treatment are socially defined concepts that are determined by the patient. The patient's preferences for or against treatment based on these indicators should be respected within the bounds of medically and ethically appropriate options. The emergency physician respects the principle of nonmaleficence by always seeking to maximize the benefits of treatment and minimize the risk of harm.

Key Practice Points

- Informed consent is a process.
- Treatment decisions can be effected by both the patient's and physician's culture, faith, and values.
- Pain is to be understood in the context of the patient's disease.
- Suspicion of opioid misuse by itself does not serve as a justification for not treating pain.
- Probe for information to help understand the patient's life.
- Agreements may be used to dispense just enough medication to treat the immediate needs of patients until they can follow up with their regular providers.
- Carefully explain the decisions being made as well as the rationale behind them.
- Be willing to change the approach if information changes.
- When giving treatment to patients at the end of their lives, always assess them for pain and delirium, as they are often confused.
- Determine the appropriate decision-maker at the beginning of the patient encounter.

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Chapter 9
Emergencies in Infectious Diseases

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Contents

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Chapter Overview

A cancer patient who visits The University of Texas MD Anderson Cancer Center Emergency Center (EC) with symptoms such as fever, hypotension, and changes in mental status will undergo an evaluation for possible sepsis. This chapter covers infectious complications in cancer patients. In it we describe specific infectious processes that most commonly affect our patient population: pneumonia, neutropenic fever, sepsis, and surgical wound infections. Infections related to the presence of catheters in various parts of the body, including central venous catheters, may be frequently associated with certain micro-organisms.

Introduction

Recognition that cancer patients with infections can present with minimal symptoms or signs suggesting infection because of defects in immune and inflammatory responses and host-defense mechanisms is important. The condition of immunocompromised cancer patients with acute infections can deteriorate very quickly. Some patients present with fever, others present with hypothermia, and still others may present with hypotension or even merely subtle changes in mental status. Clinicians who evaluate them must have a high suspicion for an infectious process and perform a detailed medical history, physical examination, appropriate diagnostic testing, quick intervention, and frequent follow-up.

When evaluating a patient with cancer, keeping in mind the five main immune defects listed below is important. Knowing the patient's specific defect is helpful in the evaluation, categorization, and management of the patient. Some patients may have more than one defect at a time and have multiple infections concurrently.

1. Defects in the mucosal and skin barriers (e.g., central venous access devices, local invasion by tumor). Such defects predispose patients to infection with bacteria or fungi colonizing the affected area.
2. Hematologic malignancy or metastatic tumor.
3. Immunoglobulin and complement deficiency. Examples are patients with multiple myeloma or chronic lymphocytic leukemia. These patients are predisposed to bacterial infections, particularly those caused by encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae.*

4. Cellular immunity defects, which can occur in bone marrow or hematopoietic stem cell transplant recipients undergoing immunosuppressive therapy for graft-versus-host disease and leukemia and lymphoma patients, including those receiving alemtuzumab or purine analogs (e.g., fludarabine, pentostatin, cladribine). These patients can have a variety of infectious processes, such as bacterial (e.g., *Listeria* and *Nocardia* infections), mycobacterial, viral (e.g., herpes group and cytomegalovirus infections), fungal (e.g., *Candida*, *Aspergillus*, *Cryptococcus*, and *Pneumocystis jirovecii* infections), parasitic, and other opportunistic infections.
5. Splenectomy patients are predisposed to infections with encapsulated organisms such as *S. pneumoniae* and *H. influenzae*.

After hematopoietic stem cell transplantation, the risk of infection is determined according to different factors, including the presence or absence of graft-versus-host disease, transplant type (increased risk with allogeneic transplants, lower risk with autologous or syngeneic transplants), graft type (highest risk with cord blood, intermediate risk with bone marrow, and lowest risk with colony-stimulating factor-mobilized blood stem cells), and use of immunosuppressive drugs. However, the risk is primarily determined by the time from transplantation, as the risk varies over time during the posttransplant course (Tomblyn et al. 2009). The three phases of opportunistic infections in allogeneic hematopoietic stem cell transplant recipients and involved factors are shown in Fig. 9.1.

The number of pathogens resistant to commonly used antibiotics has been increasing in both the general and nosocomial patient populations in recent years. Several factors have contributed to this increase, including the widespread use of antibiotics, increased number of immunocompromised hosts, and introduction of new antibiotics (Jones 2001). Before deciding on antimicrobial treatment, knowledge of the patient's immune defect or defects, history of previous and recent infections, and history of recent antibiotic use is very important. Selection of the initial antimicrobial therapy should be driven by the pathogen or pathogens and their antimicrobial susceptibility.

At our institution, the treatment approach for a cancer patient with an infectious process is often a multidisciplinary one. Collaborative interaction among members of different departments and specialties, including primary oncologists, emergency room physicians, infectious disease specialists, clinical pharmacists, intensive care unit (ICU) personnel, pulmonary physicians, surgeons, interventional radiologists, and other specialists is imperative in the fight against infectious processes that can jeopardize patients' well-being and affect the course of their cancer treatment.

Pneumonia in Patients with Cancer

Epidemiology

In 2005, pneumonia, along with influenza, was the eighth leading cause of death in the United States, the sixth leading cause of death in individuals over the age of 65 years, and the leading cause of death among infectious diseases. In cancer patients,

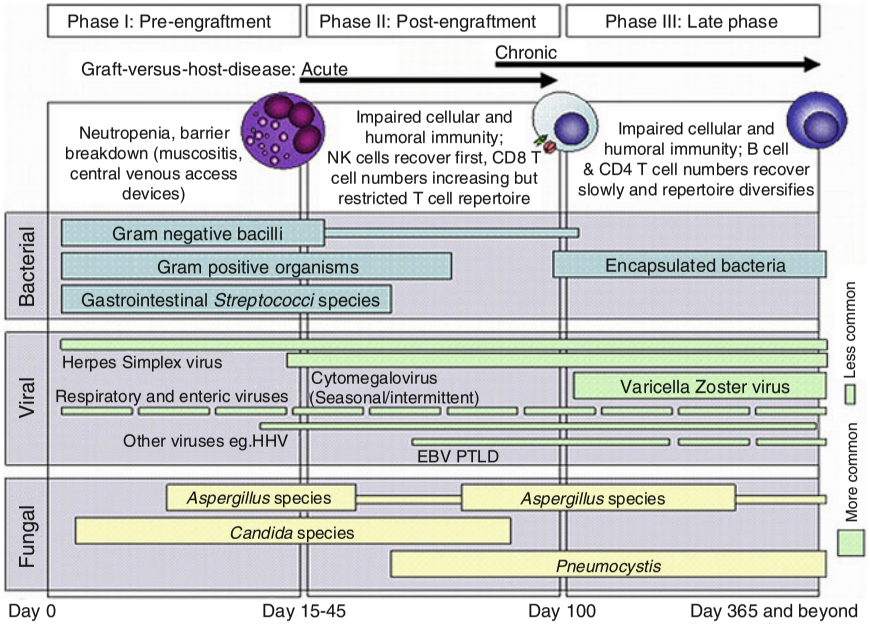

Fig. 9.1 Phases of opportunistic infections in allogeneic hematopoietic stem cell transplant recipients. *NK* natural killer, *HHV6* human herpesvirus 6, *EBV* Epstein-Barr virus, *PTLD* posttransplant lymphoproliferative disease. [Reprinted from Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: A global perspective. Biol Blood Marrow Transplant. 2009;15:1143–1238 with permission from Elsevier.]

the lung is a common site of infection, and pneumonia is the leading overall infectious cause of death.

Definitions

The typical pneumonia history and presentation of cough with or without sputum production, fever, dyspnea, and chest pain or examination finding of abnormal focal chest signs may or may not be present in a cancer patient who is immunocompromised. A profoundly neutropenic patient with a pulmonary infection may have minimal or no signs, symptoms, or physical findings of pneumonia or pulmonary infiltrates on chest radiographs.

Pneumonia is categorized according to four types.

1. Hospital-acquired pneumonia (HAP): occurs 48 h or more after admission.
2. Ventilator-associated pneumonia (VAP): develops more than 48–72 h after endotracheal intubation.
3. Healthcare-associated pneumonia (HCAP): develops in a patient with specific risk factors such as the following:
    - Hospitalization for 2 or more days within the prior 90 days
    - Residence in a nursing home or extended-care facility
    - Chronic dialysis within the last 30 days
    - Home wound care within the last 30 days
    - Home infusion therapy (including antibiotics)
    - Family member with multidrug-resistant (MDR) pathogen infection
    - Chemotherapy within the last 30 days
4. Community-acquired pneumonia (CAP): does not fit the criteria for HCAP, HAP, or VAP. At our institution, this may be pneumonia in a patient undergoing surveillance, an employee with no patient contact, or a visitor.

In the MD Anderson EC, 88 % of patients diagnosed with pneumonia have HCAP, whereas only 12 % have CAP. Recent chemotherapy, radiation therapy, or any other cancer therapy is considered a risk factor for HCAP. In comparison with patients with CAP, 82 % of whom receive treatment as outpatients, 89 % of patients who present with pneumonia are hospitalized.

Microbiology of Pneumonia in Cancer Patients

The spectrum of pulmonary infections in the cancer population depends on the underlying immunologic deficit or deficits. *Staphylococcus aureus* and *S. pneumoniae* are the most common Gram-positive organisms. In neutropenic patients, as neutropenia persists, infection with resistant Gram-negative bacteria (e.g.,

Acinetobacter, *Enterobacter*, and *Pseudomonas* species; *Stenotrophomonas maltophilia*) and fungi (e.g., *Aspergillus, Zygomyces*, and *Fusarium* species) can occur, especially in those with hematologic malignancies (Rolston 2001). Other organisms isolated from cancer patients' respiratory specimens include mycobacteria (mostly nontuberculous); *Legionella*, *Candida*, and *Nocardia* species; *P. jirovecii*; cytomegalovirus; and community respiratory viruses.

Many patients with HCAP, HAP, or VAP and some with CAP are at increased risk for colonization of and infection with MDR pathogens. Risk factors for MDR pathogen infection include exposure to antimicrobial therapy 90 days before pneumonia diagnosis, current hospitalization of 5 days or more, high frequency of antibiotic resistance (in the hospital or community), all risk factors for HCAP, and immunosuppressive disease and/or its therapy. The clinical and microbiologic features of HCAP are more similar to those of HAP and VAP than to those of CAP. In an epidemiologic retrospective cohort study, Kollef et al. (2005) analyzed 4543 patients with culture-positive pneumonia who were admitted to 59 U.S. hospitals. The distribution of pathogens varied according to the 4 types of pneumonia. Nevertheless, *S. aureus* (including methicillin-sensitive and -resistant strains) was the dominant pathogen. The incidence rate of methicillin-resistant *S. aureus* (MRSA) infection was markedly higher in patients with HCAP than in those with the other 3 types of pneumonia. Also, the proportions of patients with HCAP and VAP having *Pseudomonas* species infections (25 % and 21 %, respectively) were higher than that of patients with CAP (17 %). However, the *S. pneumoniae* infection prevalence rate was higher in patients with CAP than in those with the other 3 types of pneumonia. Although most pulmonary infections in cancer patients are caused by a single pathogen, a significant proportion can have polymicrobial infections.

Initial Assessment and Management of Pneumonia in the Cancer Patient

Diagnostic Testing

A patient's history and/or physical examination may be suggestive of pneumonia. The following initial diagnostic tests are recommended:

- Chest X-ray or other diagnostic modality, such as chest computed tomography
- Complete blood count with differential; basic chemical profile, including blood urea nitrogen, creatinine, electrolyte, serum transaminase, and glucose level measurement
- Blood cultures in all patients with pneumonia (1 set with blood from each lumen of an existing central venous catheter [CVC] and 1 or 2 peripheral blood cultures from 2 sites if the patient does not have a CVC) prior to antibiotic administration
- Sputum Gram stain and culture if the patient has a productive cough

- Arterial blood gas testing is recommended for patients with oxygen saturation less than 90 % or who are unstable
- If CAP is suspected, obtaining urine *Legionella* and pneumococcal antigens is recommended
- During seasons with a high incidence of respiratory viral infections, obtain nasal washes for respiratory syncytial virus/influenza antigens and viral cultures from patients with hematologic malignancies or neutropenia
- Patients with hematologic malignancies, including bone marrow transplant recipients, may undergo a serum galactomannan test (for diagnosis of invasive *Aspergillus* infection) and cytomegalovirus antigenemia test

Risk Assessment

Major decisions regarding management of CAP revolve around the initial assessment of its severity. Several pneumonia severity-risk stratification systems for CAP help clinicians predict mortality risk and site of care (home versus hospital, ward floor versus ICU). At MD Anderson, we recommend the use of the Pneumonia Severity Index for risk assessment (Aujesky and Fine 2008), as a retrospective case review demonstrated it to correlate better than the CURB-65 criteria with the severity of pneumonia in patients presenting to the EC (Gonzalez et al. 2014). Use of the Pneumonia Severity Index in immunosuppressed patients with pneumonia has yet to be validated.

Management

At our institution, we developed a comprehensive set of pneumonia algorithms and orders to assist clinicians in making important decisions regarding management steps such as selection of antibiotics and respiratory interventions, use of diagnostic testing, consultations with infectious disease and pulmonary specialists or members of a tobacco cessation program, and making recommendations for influenza and pneumococcal vaccines.

Selection of antibiotics is based on the type of pneumonia and relative risk of infection with a drug-resistant pathogen. The choice of order sets for pneumonia is based on the recommendations and guidelines for the management of CAP, HCAP, HAP, and VAP published by the American Thoracic Society and Infectious Diseases Society of America and on MD Anderson epidemiologic data (Fig. 9.2). We recommend obtaining the patient's antibiotic history over the previous 90 days and considering an alternative agent in a different class of antibiotics. De-escalation of antibiotics and switching to oral agents should be based on microbiologic culture results and the organism's susceptibility as well as the patients' clinical response. In patients with HCAP having clinical responses to antibiotics, the therapy duration should be 7 days. At the MD Anderson EC, a high percentage of the patients who present with pneumonia also have signs and symptoms of sepsis. Our recommendation

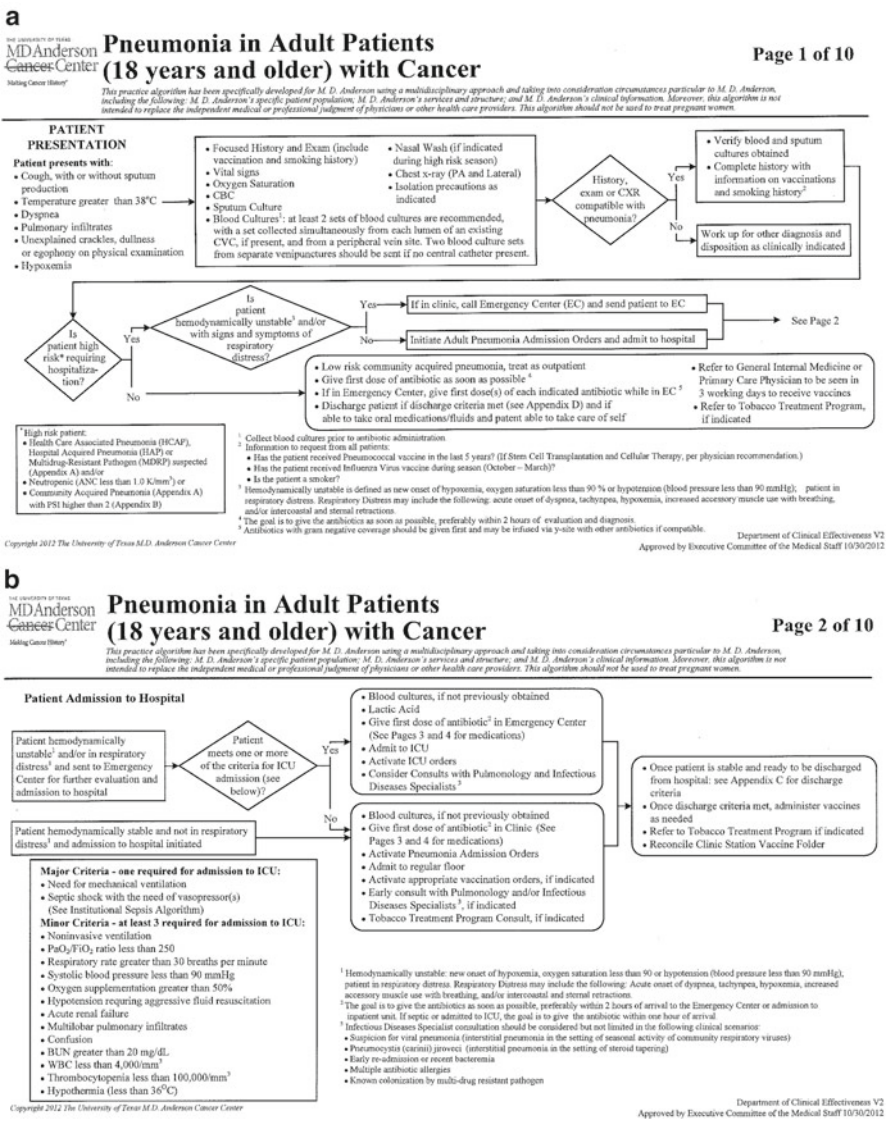

Fig. 9.2 (contined)

is to give them empiric antibiotics as soon as possible and in the first 2 h after arrival at the EC.

The antibiotic section of the MD Anderson adult pneumonia order set is divided into three options (Fig. 9.2).

- Option 1: HCAP with risk factors for MDR pathogen infection or neutropenic pneumonia.

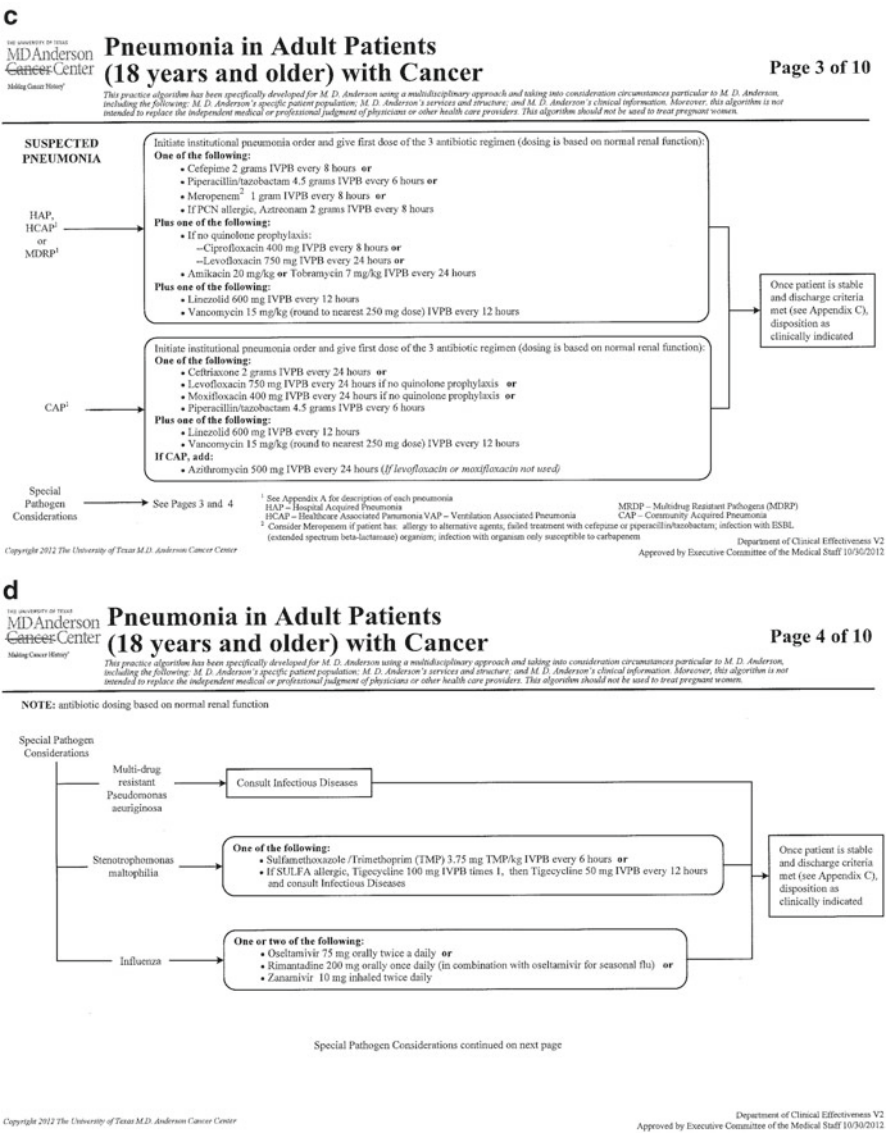

Fig. 9.2 Adult pneumonia order set [pages 1(a), 2(b), 3(c), and 4(d) of 10]

- Combination therapy should be used if the patient is likely to be infected with MDR pathogens.
- Patients at risk for Gram-negative bacterial infections should receive dual empiric antibiotic coverage.
- Patients should receive initial empiric therapy that covers MRSA at the time of HCAP diagnosis.

  - The duration of antibiotic therapy for HCAP in a patient who has a clinical response should be 7 days.

- Option 2: coverage for MRSA is recommended for patients with early-onset HAP or CAP but without risk factors for MDR pathogen infection.
- Option 3: specific recommendations are provided for patients with MDR *Pseudomonas aeruginosa*, *S. maltophilia*, or influenza infection. We recommend prompt consultation with an infectious disease specialist for patients with fungal/mold infections.

Neutropenic Fever

Febrile neutropenia is a medical emergency. Prompt evaluation and administration of empiric broad-spectrum antibiotics is required for patients with it. Even though the use of human granulocyte colony-stimulating factors such as filgrastim and peg-filgrastim in patients at risk for granulocytopenia has increased over the past few years, fever, including neutropenic fever, is still the most common presenting symptom at the MD Anderson EC. Neutropenic fever algorithms and order sets have been developed to guide clinicians in assessing and treating febrile neutropenia.

Definitions

Fever is defined as a single oral temperature of at least 38.3 °C (101 °F) or a temperature of at least 38 °C (100.4 °F) that persists for 1 h or longer. Neutropenia is defined as an absolute neutrophil count (ANC) of less than 500 cells/mm^3 or an ANC of less than 1000 cells/mm^3 that is projected to decrease to less than 500 cells/mm^3. Profound neutropenia is defined as an ANC of no more than 100 cells/mm^3.

Microbiology

In patients with neutropenic fever, knowledge of epidemiologic shifts, local microbiology, and resistance patterns is imperative to initiate effective prophylactic, empiric, and specific treatment. Bacterial infections are most common during the early phase of neutropenic fever, and Gram-positive bacteria have predominated in most cancer centers. The most common Gram-positive bacteria are viridans streptococci and *Staphylococcus*, *Enterococcus*, *Corynebacterium*, and *Bacillus* species. The most common Gram-negative bacteria are *Escherichia coli, P. aeruginosa, Klebsiella* and *Proteus* species, and *S. maltophilia.* Patients with prolonged, severe neutropenia and/or those who have been exposed to multiple broad-spectrum

antibiotics are susceptible to fungal infections. The most common fungal organisms in neutropenic febrile patients are *Candida* species, *Trichosporon beigelii*, and *Aspergillus*, Zygomycetes, and *Fusarium* species (Rolston 2004).

Risk Assessment

The risk of complications of infection must be assessed upon initial evaluation of a patient with fever. Decisions such as site of treatment (inpatient versus outpatient), type of antibiotics, and duration of treatment will depend on classification of a patient as being at high or low risk. In general, high-risk patients are those with anticipated prolonged (more than 7 days), profound neutropenia and/or significant medical conditions.

At the MD Anderson EC, patients with hematologic malignancies, who undergo hematopoietic stem cell transplantation, or with comorbidities such as hypotension, organ dysfunction, bleeding, and altered mental status who present with neutropenic fever are considered to be at high risk. The high-risk population must be given aggressive treatment and admitted to the hospital.

The Multinational Association of Supportive Care in Cancer developed a scoring system (Table 9.1) to identify febrile neutropenic cancer patients at low risk for a serious medical complication (e.g., hypotension; respiratory, cardiac, or renal failure; disseminated intravascular coagulopathy; severe bleeding). In a prospective observational study, De Souza et al. (2008) found that the Multinational Association

Table 9.1 The multinational association of supportive care in cancer risk prediction model score

Characteristic	Weight (number of points)[a]
Age <60 years	2
Outpatient status	3
Clinical status at presentation	
No severe burden of febrile neutropenia	
No or only mild symptoms	5
Moderate symptoms	3
No hypotension (systolic blood pressure >90 mm Hg)	5
No dehydration requiring parenteral fluids	3
Medical history, underlying disease, and/or comorbidity	
No chronic pulmonary disease	4
Solid tumor or hematologic malignancy without previous invasive fungal invasion	4

Reprinted from Kern W. Risk assessment and treatment of low-risk patients with febrile neutropenia. Clin Infect Dis. 2006;42:533–540. With permission from Oxford University Press

[a]The maximum theoretical score is 26. Patients with a score of 21 or greater are considered to be at low risk

of Supportive Care in Cancer risk index score has a sensitivity of 88 %, specificity of 85 %, and positive predictive value of 90.6 %. This scoring system is simple and easy to apply and may be useful in the emergency setting.

Evaluation of the Patient with Neutropenic Fever

A very important point to emphasize is that the inflammatory response to an infectious process is significantly altered in a patient with neutropenia, and the patient may not have symptoms or signs of infection or inflammation. A thorough history and complete physical examination are important, including examination of the mucous membranes, skin, catheters, and drains for sources of infection. If the patient has perianal symptoms, the perianal region is examined visually. Digital rectal examination is contraindicated.

Work-up consists of the following:

- Complete physical examination
- Complete blood count with differential; ANC; platelet count; blood urea nitrogen, creatinine, electrolyte, and CO_2 measurement; and liver function tests (total and direct bilirubin, hepatic transaminase enzyme, alkaline phosphatase, and lactate dehydrogenase level measurement)
- Lactic acid level measurement (performed in all patients who present to the EC with fever as a screening tool to identify those who may be septic)
- Urinalysis
- At least 2 sets of blood cultures (1 set with blood from each lumen of an existing CVC and 1 or 2 peripheral blood cultures if no CVC is present), urine cultures, and other cultures as indicated
- Chest X-ray
- Consideration of the Multinational Association of Supportive Care in Cancer score
- Serum galactomannan testing (for diagnosis of invasive aspergillosis) and cytomegalovirus antigenemia testing in all patients with hematologic malignancies, including bone marrow transplant recipients, admitted to the hospital; nasal washes for respiratory syncytial virus/influenza A antigen and a respiratory culture panel during seasons with a high incidence of respiratory viral infections

Outpatient Treatment of Neutropenic Fever

Low-risk patients with febrile neutropenia may be candidates for outpatient treatment. The following are the criteria for a patient to be considered for outpatient treatment at our institution:

- Solid tumor
- At least 15 years of age

- No quinolone allergy (oral regimen)
- Able to tolerate oral medications and fluids
- Does not use percutaneous enteric gastrostomy feeding as the primary route for nutrition or medication
- Temperature greater than or equal to 38.3 °C
- ANC less than or equal to 1000/mm^3
- Not currently receiving antibiotics
- Lives within 1 h of travel time from MD Anderson
- Has a 24-h caregiver
- Has access to transportation and a telephone in the residence

Administration of antibiotics for outpatient treatment of neutropenia is initiated in the EC. Specifically, the first combination or single-agent treatment is administered in the EC, and tolerance to it is observed. The treatment recommendations listed below are based on normal renal and hepatic function and must be adjusted accordingly.

Combination Therapy

- No penicillin allergy
  - Ciprofloxacin 750 mg orally twice a day PLUS
  - Amoxicillin/clavulanic acid 875 mg orally twice a day for 7 days
- Penicillin allergy
  - Clindamycin 600 mg orally 3 times a day PLUS
  - Ciprofloxacin 750 mg orally twice a day for 7 days
    OR
  - Azithromycin 500 mg orally once a day PLUS
  - Ciprofloxacin 750 mg orally twice a day for 7 days
- Monotherapy
  - Levofloxacin 750 mg orally each day for 7 days
    OR
  - Moxifloxacin 400 mg orally for 7 days

Follow-up for the Outpatient with Neutropenic Fever

Low-risk neutropenic febrile patients without contraindications for outpatient treatment undergo follow-up in the outpatient setting at the MD Anderson neutropenic clinic in what we call the Neutropenic Fever Outpatient Pathway. The patient visits the clinic on days 2, 3, and 7. A complete blood count and ANC as well as serum creatinine level measurement are performed on the days of the clinic visits,

and the patient is evaluated for any complications and tolerance of and response to the treatment. On days 4, 5, and 6, the patient receives a follow-up telephone call. Failure to have a response to the outpatient treatment, such as persistent fever after 3 days of antimicrobial therapy, requires reassessment that may result in changing or adding antibiotics but typically requires hospitalization for intravenous (IV) antibiotic infusion and further evaluation. If fever persists after 4–7 days, addition of antifungal therapy is considered (Freifeld et al. 2011).

Treatment in Neutropenic Febrile Inpatients

All high-risk patients are admitted to the hospital for intravenous antibiotic therapy.

The initial evaluation and diagnostic tests are performed as described above for outpatients. If a patient presents with initial signs and symptoms of severe sepsis or septic shock, the algorithm and order set for severe sepsis apply. A decision on antibiotic therapy will depend on multiple factors (described above in the Introduction). A multidisciplinary group of experts developed the MD Anderson Adult Neutropenic Fever order sets as a guideline to be initiated in the EC for patients admitted to the hospital. The following antibiotic recommendations are based on normal renal and hepatic function and must be adjusted accordingly.

Monotherapy: considered for patients who are clinically stable and without skin or soft tissue infections. Typical choices include:

- IV cefepime 2 g every 8 h

  OR
- IV piperacillin/tazobactam 4.5 g every 6 h
  OR
- IV meropenem 1 g every 8 h
- If penicillin allergy, refer to combination therapy below

Combination therapy

- Combination therapy should be considered for patients with tissue infections, enterocolitis, and/or perirectal infections
  - IV cefepime 2 g every 8 h
    OR
  - IV piperacillin/tazobactam 4.5 g every 6 h
    OR
  - IV meropenem 1 g every 8 h
  - If penicillin allergy, IV aztreonam 2 g every 8 h and IV vancomycin 15 mg/kg every 12 h PLUS
  - An aminoglycoside (use adjusted body weight if greater than 40 % ideal body weight) every 24 h

OR
- IV ciprofloxacin 400 mg every 8 h (if no history of quinolone allergy)

- Combination therapy should be considered for patients who have been undergoing quinolone-based prophylaxis/treatment (within 90 days), with confirmed or suspected MRSA colonization, with catheter-related bloodstream infections (CRBSIs), or with soft tissue infections
  - IV vancomycin 15 mg/kg every 12 h and IV cefepime 2 g every 8 h

    OR
  - IV piperacillin/tazobactam 4.5 g every 6 h

    OR
  - IV meropenem 1 g every 8 h
  - If penicillin allergy, IV aztreonam 2 g every 8 h and either an aminoglycoside or ciprofloxacin PLUS
  - If indicated, an aminoglycoside (use adjusted body weight if greater than 40 % ideal body weight every 24 h)

    OR
  - IV ciprofloxacin 400 mg every 8 h (if no history of quinolone allergy)
    - Combination therapy in patients with mucositis
      - IV vancomycin 15 mg/kg every 12 h PLUS
      - IV cefepime 2 g every 8 h

      OR
      - IV piperacillin/tazobactam 4.5 g every 6 h

      OR
      - IV meropenem 1 g every 8 h
      - If penicillin allergy, IV aztreonam 2 g every 8 h and IV clindamycin 900 mg every 8 h and an aminoglycoside (use adjusted body weight if greater than 40 % ideal body weight) every 24 h

- Special considerations (to be added to the choices listed above)
  - Vancomycin-resistant enterococcus (excluding that identified on rectal screening)

    IV linezolid 600 mg every 12 h

    OR
    IV daptomycin 6 mg/kg every 24 h

- MDR *Pseudomonas*
  - Add IV colistin 2.5 mg/kg every 12 h (consider infectious disease specialist consultation)

- S. maltophilia
  - Add IV sulfamethoxazole and trimethoprim 3.75 mg/kg every 6 h (maximum dose, 320 mg trimethoprim every 6 h)

    OR
  - If sulfa allergy, IV piggyback tigecycline 100 mg for 1 dose and then IV tigecycline 50 mg every 12 h

Length of Therapy

The duration of therapy for neutropenic fever depends on several factors, such as resolution of fever and the type of infection, and should be continued (IV or oral) for at least 7 days. Antibiotic use can be adjusted to the isolated micro-organism and guided by clinical findings. For example, if a patient is unstable after initiation of recommended empiric therapy, the antibacterial regimen should be re-evaluated with consideration of broadened coverage to include resistant bacteria, anaerobic bacteria, and fungi.

Empiric antifungal coverage should be considered for high-risk patients who have persistent fever after 4–7 days of broad-spectrum antibacterial therapy and no identified fever source. Investigation for an invasive fungal infection should be considered, including a thorough physical examination, computed tomography scans of the chest and sinuses, fungal serology, and appropriate cultures. Antifungal therapy should be instituted if any of these indicators of possible invasive fungal infection are identified, and consultation and close collaboration with an infectious disease specialist is highly recommended. In low-risk patients with anticipated neutropenia durations of fewer than 7 days, the risk of invasive fungal infection is small. Therefore, routine use of empiric antifungal therapy is not recommended for them. Transition from IV to oral antibiotics may be considered for clinically stable patients and those able to tolerate oral medications.

Sepsis

Patients with cancer have not only an increased risk of sepsis but also higher mortality rates than patients with sepsis who do not have cancer. Recent studies suggested that implementation of guidelines for evaluation and management of severe sepsis has decreased the mortality associated with it, with the benefits being extended to the cancer population (Pene et al. 2008). Early recognition of patients at risk for severe sepsis and early intervention for it are paramount to a successful outcome.

Definition

Participants at the consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine in 1992 created a conceptual framework to view the relationships among various manifestations of infection and

the definitions that are currently used for the evaluation and management of patients with sepsis.

Sepsis is defined as a condition in which the physician suspects an infectious process with evidence of a systemic inflammatory response syndrome that manifests as two or more of the following:

- Hyperthermia (greater than 38 °C) or hypothermia (less than 36 °C)
- Tachycardia (heart rate greater than 90)
- Tachypnea (respiratory rate greater than 20 or a partial pressure of arterial carbon dioxide less than 32 mm Hg)
- White blood cell count greater than 12,000 or less than 4000 cells/mm^3 or greater than 10 % bands

Severe sepsis refers to sepsis associated with organ dysfunction, hypoperfusion, or hypotension. The patient can have one or more of the following: alteration in mental status, hypoxemia, elevated lactic acid level, oliguria for more than 2 h, or urine formation less than 0.5 mL/kg/h. Septic shock refers to severe sepsis with hypotension that persists despite adequate fluid resuscitation. Sepsis-induced hypotension is defined as a systolic blood pressure less than 90 mm Hg, mean arterial pressure less than 70 mm Hg, or systolic blood pressure decrease greater than 40 mm Hg or fewer than 2 standard deviations below normal according to age in the absence of other causes of hypotension (Dellinger et al. 2013).

Epidemiology

Severe sepsis is a growing health care challenge, with more than 750,000 cases diagnosed annually in the United States. In a study conducted to evaluate the epidemiology of sepsis in patients with malignancy admitted to hospitals in the United States from 1979 to 2001, Pajman et al. (2006) found that patients with cancer are at greater risk for development of and death owing to sepsis than the general population. They reported that the annual incidence rate was 1465 cases per 100,000 cancer patients. The study also found that having cancer was a strong independent predictor of sepsis mortality.

Initial Assessment and Management of the Cancer Patient with Sepsis

At MD Anderson, an Adult Sepsis Management Algorithm was developed with the consensus of the Sepsis Collaborative, a multidisciplinary group of ICU and EC members, infectious disease specialists, clinical pharmacists, nurses, and others. The algorithm is based on the Surviving Sepsis Campaign international guidelines for the management of severe sepsis and septic shock published in

2008 and revised in 2013 and on specific guidelines related to MD Anderson, such as antibiotic recommendations based on institution-specific antibiograms. The EC and ICU have order sets in place to help clinicians with important medical decisions ranging from diagnostic tests to antibiotic selection and supportive measures.

The clinical presentation of sepsis can be clear in patients who appear to be very ill or have toxic effects but more difficult in patients with mild symptoms, such as those presenting with changes in mental status. The origin of the infectious process may or may not be clearly identified upon initial presentation. Obtaining a thorough history and performing a physical examination, with attention paid to all catheters, drains, and other potential sources of infection via frequent re-evaluation and monitoring, are imperative (Fig. 9.3).

The most common sites of infection origin in patients with sepsis are the respiratory tract followed by the abdomen and urinary tract. A large number of our patients have decreased heart function as a result of their cancer treatment. When available, we recommend identifying the patient's most recent ejection fraction and ventricular function as soon as possible, as it may be needed to adjust the required aggressive fluid management.

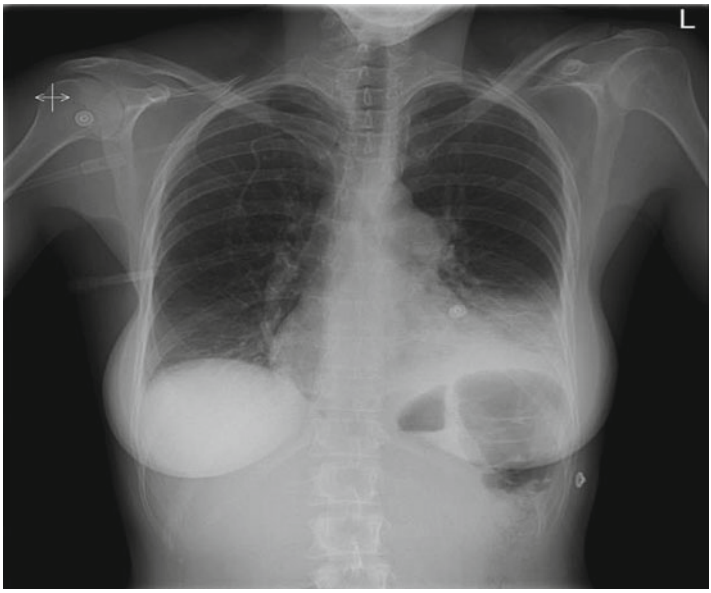

Fig. 9.3 Chest X-ray of a 41-year-old woman with acute lymphoblastic leukemia receiving chemotherapy who presented to the EC with left-sided pleuritic chest pain and hypotension. She did not have fever, was neutropenic with a total white blood count of 400/μL, and had a lactic acid level of 5.3 mmol/L. The X-ray demonstrates a left lower lobe infiltrate. This patient was septic and experienced rapid progression to septic shock with respiratory and multiple organ failure. Sputum and blood cultures were positive for *P. aeruginosa*

Diagnostic Testing

In the EC, evaluation of septic patients starts at triage. All patients presenting with sepsis and/or hypotension undergo a sepsis work-up that includes the procedures listed below.

- Laboratory tests: complete blood count; point-of-care lactic acid and arterial blood gas testing; electrolyte, blood urea nitrogen, creatinine, and carbon dioxide level measurement; coagulation profiling (prothrombin time, activated partial thromboplastin time, and D-dimer and fibrinogen level); liver function tests (total and direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and lactate dehydrogenase level measurement); glucose level measurement; cardiac panel; amylase and lipase level measurement; and urinalysis.
- Cultures: cultures of blood (1 set with blood from each lumen of an existing CVC and 1 or 2 peripheral blood cultures if no central line present), sputum, urine, and all other materials as indicated clinically.
- Use of the (1,3)-β-D-glucan assay and mannan and anti-mannan antibody assays is recommended if invasive candidiasis is suspected.
- Diagnostic imaging: chest X-ray and computed tomography scan as indicated and performed promptly to confirm the source of the infection.

Interventions/Early Goal-Directed Therapy/Bundles (Application of the 2013 Surviving Sepsis Campaign Guidelines)

Measure serum lactic acid levels and perform blood cultures before antibiotic administration.

Initial resuscitation (critical first 6 h of care)

- Begin resuscitation immediately in patients with hypotension or increased lactic acid levels (at least 4 mmol/L); do not delay pending ICU admission. This includes administration of fluid challenge (30 mL/kg) over 30 min with crystalloids and monitoring urine output (goal, greater than 0.5 mL/kg/h), central venous pressure (goal, 8–12 mm Hg or 12–15 mm Hg if intubated), and the central (superior vena cava) or mixed venous oxygen saturation target. If the central or mixed venous oxygen saturation target is not achieved (70 % and 65 %, respectively), transfusion of packed red blood cells, if required, for a hematocrit of at least 30 % and/or initiation of dobutamine infusion (maximum, 20 mg/kg/min) is recommended.
- Antibiotic therapy
  - Begin IV antibiotics as early as possible and always within the first hour after recognizing severe sepsis and septic shock

  - Administer broad-spectrum antibiotics to target likely pathogens: bacterial, fungal, and viral (considering micro-organism susceptibility patterns in the community and hospital is important)
  - Consider empiric combination therapy for MDR pathogens such as *Pseudomonas* and *Acinetobacter* species
  - Consider empiric combination therapy in neutropenic patients (Fig. 9.3)
- In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or a lactic acid level of at least 4 mmol, insertion of a CVC and arterial catheters is recommended for improved continuous hemodynamic monitoring. Patients in septic shock who do not have responses to fluids need initiation of vasopressors (first-line therapy: norepinephrine is the first choice, and epinephrine can be added to or substituted for norepinephrine) for treatment of hypotension (mean arterial pressure less than 65 mm Hg). Albumin can be considered for fluid resuscitation in patients needing substantial amounts of crystalloids. Evaluation for a specific anatomic site of infection as rapidly as possible and implementation of control measures (i.e., abscess drainage, tissue debridement, infected CVC removal) are imperative.
- Patients with severe sepsis or in septic shock are admitted to the ICU for continuation of aggressive therapy.

Other Interventions: Supportive Therapy

- Administer IV hydrocortisone at a maximum dosage of 200 mg/day in divided doses for septic shock in adults when hypotension persists after fluid resuscitation and use of vasopressors.
- Perform a red blood cell transfusion when the hemoglobin concentration is less than 7 g/dL to target a hemoglobin level of 7–9 g/dL (once tissue hypoperfusion has resolved or in the absence of acute hemorrhage, myocardial ischemia, or severe hypoxemia).
- Use an IV insulin protocol to maintain adequate glycemic control.
- Administer stress ulcer prophylaxis with an H2 blocker or proton pump inhibitors in patients who have risk factors for bleeding.
- Prevent excessive inspiratory plateau pressures in patients undergoing mechanical ventilation.

Surgical Wound Infections

Surgical wound infections result from bacterial or fungal contamination of the structures underlying the compromised integumentary system and are affected by multiple factors, including immune system compromise owing to comorbid

conditions, treatment modalities, pre-existing colonization, and exposure to resistant micro-organisms as well as the surgical procedure itself. In the cancer patient, all of these factors are relevant. In addition to the effects of previous or ongoing therapies, cancer patients may be neutropenic or immunocompromised owing to steroid use or their disease. Also, patients have increased potential for colonization with vancomycin-resistant enterococci and MRSA owing to prolonged exposure to a hospital or clinical environment. Surgical interventions and anesthesia time can be prolonged owing to the extent and location of disease. Major surgeries such as tumor debulking have increased the risk of hematoma formation and vascular compromise owing to the length of time necessary for optimal outcome. Additionally, large tumors are associated with tumor necrosis, increasing the risk for presurgical establishment of a microbial infection in the necrotic tissue. Pre-exposure of patients to antibiotics to prevent infections in those with neutropenia or for treatment of bacterial infections can lead to the development of antibiotic-resistant bacteria.

We perform close monitoring of cancer patients preoperatively and postoperatively to identify potential sources of infection. The patient and family are educated in infection prevention as well as in recognizing signs and symptoms of developing infections. This allows for increasingly rapid identification of early infection so that treatment can begin. Once an infection is identified, cultures of the wound and blood are obtained, and empiric use of broad-spectrum antibiotics is begun based on current institutional data, the infection site, and the surgical procedure. Evaluation for abscess formation includes use of computed axial tomography and ultrasound. We use a multidisciplinary approach to management of postsurgical infections. Consultations include those with interventional radiologists for involved abscess drainage and infectious disease physicians for assistance in management of antibiotic or antifungal coverage for optimal treatment with adjustment of coverage based on culture results. Further surgical procedures for additional resection and debridement are performed, if necessary. Our wound/ostomy department provides expert care of surgical incisions using the latest techniques to promote healing. Throughout the process, the patient and family are educated and involved in the patient's care to ensure optimum management while in the hospital and after discharge.

Infections Related to Long-Term CVC Use

CVCs are widely used for both inpatient and outpatient management of cancer by facilitating chemotherapy, supportive therapy, and blood sampling. Use of CVCs is a major cause of morbidity and mortality in cancer patients and a leading cause of bloodstream infections in this population.

Different types of long-term CVCs are currently used in cancer patients and are designed to remain in place for more than 14 days. These include nontunneled CVCs, surgically implanted tunneled CVCs, totally implanted subcutaneous ports, and peripherally inserted central catheters. Infections related to CVC use can be grouped into 6 categories.

1. Catheter colonization: growth of organisms in culture of the catheter tip or hub without associated bloodstream infection
2. Exit-site infection: erythema, induration, or tenderness within 2 cm of the catheter exit site and/or purulent drainage
3. Phlebitis: erythema, induration, pain, or tenderness along the tract of a catheterized vein
4. Tunnel infection: erythema, induration, or tenderness more than 2 cm from the catheter exit site along the subcutaneous tract of a tunneled catheter
5. Pocket infection: infected fluid in the subcutaneous pocket of an implanted port, sometimes associated with erythema, induration, or tenderness of the overlying tissue
6. CRBSI

Pathophysiology and Etiology

Most CRBSIs originate at the CVC insertion site, hub (the threaded plastic connection at the end of the catheter), or both. The microbes that most commonly cause CRBSI are coagulase-negative staphylococci, *S. aureus*, *Candida* spp., and enteric Gram-negative bacilli.

Diagnosis

For an exit-site or tunnel infection, physical examination is diagnostic, and exit-site culture often correlates with the pathogen causing the infection. Establishing a diagnosis of CRBSI based on clinical findings is often difficult, however, as inflammation and purulent discharge are usually absent at the exit site. Fever, the most sensitive clinical finding, is nonspecific. In the absence of other identifiable sources of infection, blood cultures that are positive for coagulase-negative staphylococci, *S. aureus*, *Candida* spp., or enteric Gram-negative bacilli should raise the suspicion for CRBSI.

When CRBSI is suspected, paired blood cultures drawn from the catheter and a peripheral vein should be obtained prior to initiation of antibiotic therapy, and the culture bottles should be marked to reflect the site of origin. CRBSI is defined as a colony count of microbes that have grown in blood obtained through the catheter hub at least 3-fold greater than the colony count in blood obtained from a peripheral vein. If a quantitative blood culture technique is unavailable, CRBSI may be defined using the differential time to positivity technique: detection of microbial growth in a blood sample drawn from a catheter hub at least 2 h before detection of it in a blood sample obtained from a peripheral vein.

If the catheter is removed because of a suspected CRBSI, the catheter tip should be cultured. Growth of greater than 15 colony-forming units from a 5-cm segment

of the catheter tip according to the roll plate technique or of greater than 100 colony-forming units according to sonication broth culture reflects catheter colonization. When catheter infection is suspected and an exudate is observed at the catheter exit site, the exudate should be swabbed for culture.

General Management of Catheter-Related Infection

Antibiotic therapy is often initiated empirically for suspected catheter-related infection. The initial choice of antibiotics depends on the severity of illness, risk factors for infection, and likely pathogens involved. Coagulase-negative staphylococci are the most common causes of catheter-related infections, and most of them are resistant to methicillin. Vancomycin is recommended for empirical therapy in health care settings with increased prevalence of methicillin-resistant staphylococci. Alternative agents such as daptomycin and linezolid should be used for MRSA isolates with vancomycin minimum inhibitory concentration values greater than 2 μg/mL. Empiric combination antibiotic coverage for Gram-negative bacilli (such as a fourth-generation cephalosporin, β-lactam/β-lactamase combination, or carbapenem with or without an aminoglycoside) should be based on local antimicrobial susceptibility data, the severity of the disease, or the presence of a femoral catheter. Empiric combination antibiotic coverage for MDR Gram-negative bacilli, such as *P. aeruginosa*, should be initiated when a CRBSI is suspected in a patient who is neutropenic, septic, or known to be colonized with such pathogens. Empiric therapy for catheter-related candidemia (e.g., that with an echinocandin) should be considered for septic cancer patients with risk factors including total parenteral nutrition, prolonged exposure to broad-spectrum antibiotics, a hematologic malignancy, receipt of a stem cell transplant, femoral catheterization, and colonization of *Candida* spp. at multiple sites.

Catheters should be removed from patients with severe sepsis, suppurative thrombophlebitis, endocarditis, or CRBSI that persists (with persistent positive blood cultures or fever) despite more than 72 h of antimicrobial therapy to which the microbes are susceptible. Catheters also should be removed from patients with CRBSI caused by *S. aureus*, *P. aeruginosa*, fungi, or mycobacteria. Catheter removal should be considered for patients with CRBSI owing to less virulent organisms that are difficult to eradicate, such as *Bacillus*, *Micrococcus*, and *Propionibacterium* species, in the setting of multiple positive blood cultures (ruling out blood culture contamination). If the patient has a single blood culture positive for coagulase-negative staphylococcus, additional blood cultures should be obtained through the catheter and from a peripheral vein before starting antibiotic therapy or removing the catheter to verify that the patient has a true bloodstream infection and that the catheter is its likely source.

Antibiotic therapy duration depends on the isolated organism and extent of infection. For uncomplicated CRBSI, catheter removal followed by 4–6 weeks of antibiotic therapy traditionally has been recommended for *S. aureus* infections to prevent

hematogenous complications. Coagulase-negative staphylococcus infections should be treated with systemic antibiotics for 10–14 days. *Enterococcus* and Gram-negative infections should be treated with systemic antibiotics for 7–14 days. *Candida* infections should be managed with removal of the catheter and 14 days of antifungal therapy after the first negative blood culture. In patients in whom the CVC is left in place, the CVC should be removed if clinical deterioration or persistent or relapsed bacteremia is observed, and work-up for complicated infections should be pursued.

Instilling antimicrobials via a catheter and leaving the solution to dwell (i.e., antibiotic lock therapy) has increased the success rate in clearing bacteremia and allowed for retention of catheters. Antibiotic lock therapy is used in conjunction with systemic antibiotic therapy and involves instillation of a high concentration of an antibiotic to which the particular organism is susceptible into the catheter lumen. Antibiotic lock therapy should be used for CRBSI if the catheter is to remain in place; otherwise, antibiotics should be administered through the colonized catheter. In either case, repeat blood cultures should be obtained 72 h after the initiation of appropriate therapy, and the catheter should be removed if cultures remain positive. Antibiotic lock therapy should be used in conjunction with systemic antibiotics, with both regimens administered for 7–14 days. Guidelines for antibiotic lock therapy as well as recommendations for pathogen-specific treatment were provided by Mermel et al. (2009).

A tunnel infection or port abscess (pocket infection) should be managed with removal of the device and 7–10 days of antibiotic therapy. Four to 6 weeks of antibiotic therapy should be given to patients with bacteremia or candidemia persisting more than 72 h after catheter removal or in the presence of an intravascular focus of infection such as infective endocarditis or suppurative thrombophlebitis. A diagnosis of suppurative thrombophlebitis is suspected with persistently positive blood cultures and confirmed by the demonstration of a thrombus in radiographic testing. Surgical resection of the involved vein should be limited to patients with purulent superficial veins, failure of appropriate antibiotic therapy, or extension of the infection beyond the vessel wall. The use of heparin in the management of suppurative thrombophlebitis remains controversial.

Key Practice Points

- More than 85 % of patients who present to the MD Anderson EC with pneumonia have HCAP. The clinical and microbiologic features of HCAP are more similar to those of HAP and VAP than to those of CAP.
- At our institution, 89 % of the patients diagnosed with pneumonia are hospitalized. In comparison, 82 % in the community have CAP and receive treatment as outpatients.
- The Pneumonia Severity Index is the preferred scoring system for cancer patients with pneumonia who are evaluated in the EC. Validation of this index in immunocompromised patients is needed.

- Cancer patients with pneumonia should receive initial empiric therapy that covers MRSA, and those at risk for Gram-negative bacterial infections should receive dual empiric antibiotic coverage at the time of HCAP diagnosis.
- Patients with neutropenia may not present with the typical signs and symptoms of infection that are present in immunocompetent individuals. Vigilance is important when evaluating a patient with neutropenia.
- Individual institutions should develop guidelines for the treatment of different infectious processes based on local epidemiology and their patterns of susceptibility and resistance.
- The microbes that most commonly cause CRBSIs are coagulase-negative staphylococci, *S. aureus*, *Candida* spp., and enteric Gram-negative bacilli.
- A CRBSI should be considered when a patient presents with signs or symptoms of sepsis with or without fever, particularly a severely immunocompromised patient.
- When a CRBSI is suspected, paired blood cultures drawn from the catheter and a peripheral vein should be obtained prior to initiation of antibiotic therapy.
- In a patient with a CRBSI in whom the CVC is left in place, the CVC should be removed if he or she has clinical deterioration or persistent or relapsed bacteremia.
- Adherence to Surviving Sepsis Campaign recommendations can improve survival.

Suggested Readings

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Chapter 10
Hematologic Emergencies

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Chapter Overview

Hematologic emergencies are acute, life-threatening events. Cancer, its treatments, and its baseline comorbidities can independently or collectively lead to hematologic emergencies requiring quick recognition, prompt diagnosis, and swift delivery of therapeutic interventions by frontline clinicians. The hematologic emergencies frequently encountered in cancer patients described in this chapter include venous thromboembolism (VTE), hyperviscosity syndrome (HVS), anemia, thrombocytopenia, acute hemorrhage, and transfusion reactions.

Introduction

Hematologic abnormalities are the most common medical issues in patients with all types of cancer. Most of these problems are straightforward or chronic, such as chemotherapy-related bone marrow suppression presenting as anemia and thrombocytopenia. However, some are acute, complex, and life-threatening, presenting as bona fide emergencies. Examples are pulmonary embolism (PE), leukocytosis in patients with acute leukemia, and intracranial hemorrhage. Compounding their complexity is the fact that diagnosis and management of hematologic emergencies often involve several specialists, including internal medicine physicians, hematologists, oncologists, procedure-based specialists, and surgeons. Not uncommonly, multidiscipline collaborations are required. Therefore, providing a practical integrated resource for clinicians in dealing with these emergencies is the goal of this chapter.

The two extreme pathologic manifestations of hematologic emergencies are thrombosis and bleeding. Under the first two topics in this chapter—VTE and HVS—we describe the thrombotic processes and their clinical presentations, diagnosis, and treatments. Under the next three topics—anemia, thrombocytopenia, and acute hemorrhage—we discuss the conditions that may lead to or be a consequence of bleeding. Clinical descriptions, pathogenesis, differential diagnosis, diagnostic evaluation, and early management are reviewed and summarized in quickly referenced tables. As part of the common interventions for hematologic emergencies, transfusion of the affected blood component can involve immunologic and nonimmunologic phenomena that range from benign to catastrophic. Under the last topic, we review the spectrum of transfusion reactions and treatments. We hope that this chapter provides understanding and early recognition of these common hematologic emergencies in cancer patients, leading to prompt diagnosis, early therapeutic intervention, and, thus, successful outcomes.

Acute Deep Venous Thrombosis and Pulmonary Embolism

VTE, including both deep venous thrombosis (DVT) and PE, is a major complication of cancer. Specifically, VTE is the second leading cause of death in patients with cancer (Lyman et al. 2007). The risk of VTE in patients with cancer is 4- to 8-fold

higher than that in individuals without it. Furthermore, the risk of VTE is greatest in the first year, especially the first few months, after the cancer diagnosis (Blom et al. 2005; Chew et al. 2006). The risk of VTE is very high in patients who present with metastatic cancer. Certain malignancies are associated with an increased VTE risk (e.g., pancreatic, gastric, colon, brain, kidney, ovarian, prostate, hematologic, lung) (Chew et al. 2006). Use of certain medications to treat cancer, such as tamoxifen, erythropoietin, thalidomide, lenalidomide, and bevacizumab, has been associated with a high rate of VTE (Chew et al. 2006).

Clinical Manifestations

Classical symptoms and signs of DVT are pain, swelling, redness, and warmness in the affected extremity or area. Physical examination may reveal a palpable and tender cord, engorged superficial vein, painful and cyanotic limb if acute, and nearly total venous occlusion. Common symptoms of acute PE include sudden-onset dyspnea, pleuritic chest pain, cough with or without hemoptysis, wheezing, and syncope in severe cases. Common signs include tachypnea, tachycardia, rales or pleural rubs, an accentuated pulmonic component of the second heart sound (P2), jugular venous distension, and hypotension in severe cases. Of note is that the diagnosis is proven in less than 25 % of cancer patients who present with a high clinical suspicion for VTE, whereas more than half of cancer patients with proven acute or subacute VTE have no typical symptoms or signs, with many patients having no symptoms at all.

Laboratory findings are nonspecific and include leukocytosis, an increased erythrocyte sedimentation rate, and an elevated serum lactate dehydrogenase (LDH) level in patients with VTE. Brain natriuretic peptide and troponin levels are often increased in patients with significant PE, and these increased levels are associated with adverse outcomes (Meyer et al. 2000; Sohne et al. 2006). Arterial blood gas analysis usually reveals hypoxemia, hypocapnia, respiratory alkalosis, and elevated A-a gradients in patients with acute PE. The level of D-dimer, a degradation product of cross-linked fibrin, is often elevated in cancer patients with or without VTE, limiting its use in the diagnosis of VTE in cancer cases (Carrier et al. 2008).

Electrocardiographic changes are common but nonspecific in patients with acute PE. The most common of these changes are sinus tachycardia and nonspecific ST- and T-wave abnormalities. Other electrocardiographic abnormalities are less common and include atrial fibrillation/flutter, right bundle branch block, precordial T-wave inversion, and inferior Q waves.

Chest X-rays can be normal, but more than 80 % of patients with acute PE have some radiographic changes resembling cardiomegaly, atelectasis, parenchymal abnormalities, hemidiaphragmatic elevation, and pleural effusion (Stein et al. 1991).

Diagnosis of VTE

Because the symptoms and signs of VTE are nonspecific, variable, and common in patients with and without VTE, accurate diagnosis or exclusion of VTE relies on objective imaging studies. However, a comprehensive history, a thorough physical examination, routine laboratory testing, electrocardiography, and chest X-rays are useful in suggesting alternative diagnoses, indicating the general severity of the patient's illness and, most importantly, assessing the clinical probability of VTE. Clinical prediction rules (such as the Wells and Geneva scores) (Wells et al. 2001; Le Gal et al. 2006), which have been used successfully to quantitatively assess the clinical probability of DVT and PE in the general population, should not be used in cancer patients because of a lack of validation.

Duplex compression ultrasonography (US) is widely recognized as the most cost-effective and the preferred imaging modality for the diagnosis of DVT in both the lower and upper extremities. It is most sensitive (greater than 97 %) and specific in detecting symptomatic proximal DVT but markedly less sensitive in detecting distal DVT (53–73 %) and asymptomatic proximal DVT (62 %). Negative US results in patients with a high clinical suspicion for DVT should be interpreted cautiously. In such cases, alternative imaging studies or repeat US within a week should be performed.

Contrast venography, an invasive procedure, is the historic and de facto gold standard for the diagnosis of DVT. It has been largely replaced by noninvasive diagnostic modalities such as US, however. Contrast venography is now very rarely used and reserved for situations such as when noninvasive studies are not feasible or the results of those studies are equivocal or discordant with clinical suspicion.

Computed tomography venography (CTV) has greater sensitivity and specificity than US in the evaluation of proximal DVT (Sampson et al. 2007; Thomas et al. 2008). It has several advantages over US, such as identification of extravascular sources of extrinsic compression that may underlie the cause of DVT as well as better detection of thrombi in pelvic veins (proximal external iliac vein, iliac vein, and inferior vena cava [IVC]). However, it has problems similar to those for contrast venography, such as exposure to ionizing radiation and iodinated contrast media, and it cannot be performed at bedside.

Magnetic resonance venography (MRV) has not been studied as widely as US or CTV. However, several clinical studies have demonstrated that MRV is as sensitive and specific as US or CTV when evaluating proximal DVT (Sampson et al. 2007). MRV does not expose the patient to ionizing radiation or iodinated contrast media. Also, like CTV, MRV has the advantages over US of detecting pelvic DVT, delineating extravascular anatomy, and identifying nonthrombotic conditions that may mimic DVT. Cost, availability, and use of unsafe devices are among the many limitations of and contraindications for MRV.

Radionuclide venography is a noninvasive modality that is not as sensitive or specific as US, but it is still a reasonable alternative to US, CTV, and MRV when those studies are not feasible. Because radionuclide venography has yet to be validated

in comparison with contrast venography or US in large prospective clinical trials, both positive and negative radionuclide venography findings should be confirmed using other diagnostic modalities if these findings are not strongly concordant with clinical suspicion of DVT.

Computed tomography pulmonary angiography (CTPA) has largely replaced ventilation and perfusion and become the primary modality for diagnosis of PE. With improvements in this technology, new multidetector computed tomography scanners have become widely used and exhibited high sensitivity in detecting PE, particularly in the peripheral pulmonary arteries. Therefore, a negative result of this sensitive modality is generally accepted as excluding PE without the need for additional imaging.

Pulmonary angiography, the reference standard for diagnosis of PE, is now used rarely and only when coupled with clot extraction or thrombolytic therapy.

V/Q scintigraphy (V/Q scan) is much less sensitive and specific than CTPA in detecting PE. More than 50 % of patients must undergo additional testing after a V/Q scan because of nondiagnostic results. Therefore, V/Q scans should be reserved for patients with contraindications for CTPA, such as uncorrectable contrast medium allergies and significant renal insufficiency. A V/Q scan should be used if CTPA is not available or impossible in patients who are severely obese. Interpretation of V/Q scan results for cancer patients should be correlated with the clinical probability of PE before testing. A high-probability V/Q scan will confirm the diagnosis of PE unless the patient's clinical probability is low. Also, a normal V/Q scan safely excludes acute PE in patients whose clinical probability is not high. However, a low-probability V/Q scan cannot be interpreted as negative for PE because 40 % of patients with low-probability scans but high clinical suspicion have PE (PIOPED Investigators 1990). Therefore, when a V/Q scan is nondiagnostic (low or moderate probability), additional testing, such as lower extremity US or CTPA, is necessary to confidently exclude or diagnose VTE.

Treatment of Acute VTE

The goals of VTE treatment are to prevent death and recurrence and minimize long-term morbidity. Because most VTE deaths result from recurrent PE within the first few hours after the initial event, effective antithrombotic therapy should be instituted as quickly as possible to decrease the likelihood of death (Carson et al. 1992). Therefore, empiric anticoagulant therapy should be started during the diagnostic evaluation if the physician has a high clinical suspicion of VTE and the patient does not have an excessive risk of bleeding.

Supportive care, such as supplemental oxygen, intravenous (IV) fluid, mechanical ventilation, and vasopressors, should be provided as necessary to stabilize patients to complete their diagnostic evaluations and confirm diagnoses. If PE is confirmed, the patients should undergo risk stratification at diagnosis by using readily available validated risk-assessment tools, such as the Pulmonary Embolism Severity Index

Table 10.1 PESI

Adverse outcome predictor	Outcome point score
Age in years	1 per year
Male sex	+10
Cancer	+30
Heart failure	+10
Chronic lung disease	+10
Heart rate ≥110 bpm	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate ≥30 breaths per minute	+20
Temperature <36 °C	+20
Altered mental status	+60
Arterial oxygen saturation <90 %	+20

PESI score ≤85: low risk, 2 % mortality rate at 90 days

PESI score >85: high risk, 19 % mortality rate at 90 days

(PESI) (Table 10.1) (Donze et al. 2008). Acute VTE can be safely and effectively treated on an outpatient basis. However, because of increased risk of an adverse outcome, initial anticoagulation therapy should be started in the hospital for patients with PESI scores greater than 85 or patients with the following conditions: severe PE or severe symptomatic DVT; a high risk of bleeding; thrombocytopenia; surgery within 7 days; impaired heart, lung, liver, or kidney function; medical noncompliance; or lack of family support. Patients with PESI scores greater than 85 also should have their right ventricular sizes and functions checked using echocardiography or reviews of computed tomography angiography. Thrombolytic therapy should be considered for patients with massive PE or submassive PE with moderate or severe right ventricular enlargement or dysfunction and without a high risk of bleeding. Embolectomy should be considered for patients with hemodynamic instability, a high risk of bleeding, or other contraindications for thrombolytic therapy.

Anticoagulation has been the mainstay of treatment of VTE in cancer patients with the goal of preventing thrombus propagation, which may lead to a fatal PE, pulmonary hypertension, and chronic lower extremity stasis and ulcers. Contraindications for anticoagulation are active bleeding, recent central nervous system bleeding, an intracranial or spinal lesion at high risk for bleeding (e.g., central nervous system metastases of melanoma, choriocarcinoma, thyroid cancer, renal cell cancer), and very recent major surgery. Other relative contraindications for anticoagulation include chronic bleeding, thrombocytopenia or platelet dysfunction, underlying coagulopathy, and a high risk of falls. Like with thrombolytic therapy, use of anticoagulation therapy should be justified according to the patient's cancer status and overall therapeutic and palliative goals.

Anticoagulation therapy for acute VTE is performed in 2 phases: (1) initial treatment for 3–9 months according to the American College of Chest Physicians guidelines and (2) determination of the need for extended anticoagulation to reduce

Table 10.2 Commonly used anticoagulants

Anticoagulant	Route and regimen	Situations for use
Vitamin K antagonist		
Warfarin	PO	VTE, atrial fibrillation, and mechanical valve
Factor Xa inhibitors		
Rivaroxaban	PO daily	VTE and atrial fibrillation
Apixaban	PO daily	VTE and atrial fibrillation
Fondaparinux	SC 5–10 mg daily	Adjust per CrCl and body weight
Direct thrombin inhibitors		
Dabigatran etexilate	PO	Atrial fibrillation
LMWHs		
Enoxaparin	SC 1 mg/kg every 12 h	Acute PE and symptomatic DVT
	SC 1.5 mg/kg daily	VTE, alternative to 1 mg/kg every 12 h
	SC 1 mg/kg daily	CrCl < 30 mL/min
Dalteparin	SC 100 U/kg every 12 h	Acute PE and symptomatic DVT
	SC 200 U/kg daily	DVT treated on an outpatient basis
Unfractionated heparin	80-U/kg IV bolus then 18 U/kg/h IV adjusted to twice the control aPTT	Acute VTE with high risk of bleeding or need for invasive procedures

PO by mouth, *SC* subcutaneous, *CrCl* creatinine clearance rate

the risk of recurrent VTE in patients with ongoing identifiable risk factors or idiopathic/unprovoked VTE (Kearon et al. 2012). Initial anticoagulation therapy for acute VTE consists of administration of a parenteral anticoagulant to achieve an immediate antithrombotic effect, including subcutaneous injection of low-molecular-weight heparins (LMWHs) or IV infusion of weight-adjusted unfractionated heparin or oral rivaroxaban (Table 10.2). Agent selection should be based on the characteristics of the individual drug (half-life, mode of administration, reversibility, and cost) and the patient's clinical situation (inpatient, outpatient, renal function, pending surgery, and pending thrombolytic therapy).

LMWHs are the preferred agents for initial therapy for acute VTE in most cancer patients. However, IV unfractionated heparin should be considered if rapid reversibility is needed, the patient will receive thrombolytic therapy, or the patient is morbidly obese or has significant renal insufficiency. LMWH given twice a day is preferred as the initial anticoagulation therapy in cancer patients with acute PE or severe symptomatic DVT. Dalteparin and enoxaparin should be used with caution in patients with creatinine clearance less than 30 mL a minute, whereas fondaparinux and tinzaparin use should be avoided in cancer patients with creatinine clearance less than 30 mL a minute. If feasible, anti-factor Xa activity should be monitored. LMWH dosing is adjusted to achieve optimal anticoagulation in these high-risk patients.

Maintenance anticoagulation therapy is required for cancer patients diagnosed with acute VTE: at least 3–6 months for those with DVT and at least 6–12 months for those with acute PE. However, use of anticoagulation therapy for an indefinite

duration should be considered for patients with active cancer or other persistent risk factors. According to multiple national and international guidelines, LMWHs are the preferred agents for chronic anticoagulation for the first 6 months in cancer patients who have symptomatic VTE because anticoagulation with these agents is associated with superior outcomes in patients with solid tumors and symptomatic VTE (Lee et al. 2003; Kearon et al. 2012).

Oral vitamin K antagonists (e.g., warfarin) remain reasonable treatment options for VTE when patients are unable to take LMWHs for a variety of reasons (adverse reactions, severe renal insufficiency, cost, or patient preference) or have completed 6 months of anticoagulation therapy with an LMWH. The initial dose of warfarin for most cancer patients with VTE should be no more than 5 mg daily. When warfarin use is initiated, parenteral anticoagulant administration for initial anticoagulation should be continued for at least 5 days and until the international normalized ratio (INR) has been within the therapeutic range for 24 h. The prothrombin time (PT) and INR should be checked at least twice a week in the first 2 weeks of treatment with warfarin until the INR is stabilized within the therapeutic range (2–3). The warfarin dose is then titrated based on the weekly or monthly INR.

IVC filters should only be used for treatment of acute VTE in cancer patients when anticoagulation is absolutely contraindicated or has failed. IVC filters also can be considered for patients with compromised cardiopulmonary function in whom another PE may be lethal. Other indications include prevention of PE during thrombolytic therapy or embolectomy for DVT. Permanent IVC filters should be used in patients with long-term contraindications for anticoagulation therapy, such as cerebral hemorrhage and high-risk brain metastases. In contrast, patients with temporary conditions requiring IVC filtration, such as surgery and trauma, should receive temporary retrievable IVC filters with strict follow-up for timely removal. Anticoagulation or concomitant anticoagulation therapy should be used as soon as the contraindications for this therapy resolve.

Thrombolytic therapy accelerates lysis of acute VTE and improves important physiologic parameters, such as right ventricular function and pulmonary perfusion. However, thrombolysis has not conclusively demonstrated a mortality benefit or been studied extensively in cancer patients with acute PE or VTE. Thrombolytic therapy is justified for hemodynamically unstable patients with massive PE or submassive PE along with evidence of moderate or severe right ventricular enlargement or dysfunction. Persistent hypotension owing to massive PE is the most widely accepted indication for thrombolytic therapy (Kearon et al. 2012).

Because thrombolytic therapy is associated with an increased risk of major hemorrhage, it should be considered only after PE is confirmed. If thrombolytic therapy is anticipated, such as with a patient who presents with a high clinical suspicion of PE and low blood pressure, any unnecessary invasive procedure should be avoided, and IV administration of unfractionated heparin but not LMWH should be considered for the initial anticoagulation while waiting for an imaging study to confirm the diagnosis. IV administration of 100 mg of alteplase over 2 h is the recommended thrombolytic regimen for PE in patients judged to be appropriate candidates for thrombolysis.

Thrombectomy and embolectomy can be performed via a catheter or surgically. Like thrombolytic therapy, embolectomy in cancer patients has yet to be studied in prospective clinical trials. Embolectomy should be considered when a cancer patient has massive PE or submassive PE with right ventricular dysfunction for whom thrombolytic therapy is justified but fails or is contraindicated. Similarly, thrombectomy is occasionally used in cancer patients with proximal occlusive DVT associated with significant swelling and symptoms for whom thrombolytic therapy fails or is contraindicated.

HVS

HVS is a clinical emergency consisting of increased blood viscosity resulting from increased levels of serum immunoglobulins (particularly IgM) as seen with diseases such as Waldenström macroglobulinemia and multiple myeloma. Less commonly, HVS can result from increased numbers of cellular blood components, such as red blood cells (RBCs) in polycythemia vera cases, platelets in thrombocytosis cases, and white blood cells (WBCs) in leukemia cases. Increased blood viscosity impedes capillary blood flow, leading to ischemia and organ dysfunction and resulting in a myriad of clinical manifestations: spontaneous mucous membrane bleeding, visual disturbances, and neurologic impairment. Other clinical complications include thrombosis, hypertension, heart failure, pulmonary congestion, and renal failure (Adams et al. 2009).

Serum viscosity (usually greater than 4 cP) is diagnostic in evaluating HVS when the increased viscosity is concomitant with characteristic symptoms, although serum viscosity measurements do not correlate well with symptoms or clinical findings. Other laboratory findings in HVS cases include rouleau formation on peripheral blood smears and a globulin gap of four or greater in multiple myeloma cases. Abnormal metabolic panels and electrolyte levels are common in patients with HVS.

The goal of treatment of HVS is to reduce plasma viscosity by removing excess cells or circulating complexes. Pending definitive therapy for underlying disease, supportive care should be initiated for the complications of HSV, including support for blood loss, central nervous disorders, cardiovascular effects, and metabolic imbalances. Plasmapheresis, the treatment of choice for acute severe HVS caused by paraproteinemia, rapidly reduces plasma viscosity by removing immunoglobulins, especially IgM, from the circulation, resulting in prompt alleviation of symptoms. This treatment is repeated daily until symptoms subside. If plasmapheresis is not available, vigorous IV hydration and withdrawal of 100–200 mL of blood may be performed to relieve symptoms in cases of acute HVS (Geraci et al. 1990). Of note is that plasmapheresis does not affect the underlying disease process; treatment of the underlying etiology should be initiated as soon as possible. Blood cell transfusions should be avoided until serum viscosity is reduced, as transfusion can increase the viscosity and worsen symptoms. If transfusion of packed RBCs (PRBCs) is necessary, it should be performed slowly and cautiously.

Hyperleukocytosis

Hyperleukocytosis is defined as a peripheral WBC count greater than 100×10^9/L. Leukostasis, or symptomatic hyperleukocytosis, is a medical emergency most commonly seen in patients with acute myeloid leukemia but is also associated with chronic myeloid leukemia in blast crisis, acute lymphoblastic leukemia, and chronic lymphocytic leukemia. Approximately 10–20 % of patients diagnosed with acute myeloid leukemia present with hyperleukocytosis. Large numbers of intravascular leukemic blasts increase blood viscosity and cause leukocyte aggregation and clumping in the microvasculature, resulting in end-organ damage and life-threatening complications. Leukostasis is diagnosed in a leukemia patient with a WBC count greater than 100×10^9/L and respiratory or neurologic manifestations.

The primary clinical symptoms of leukostasis are related to involvement of the lungs and central nervous system (Lester et al. 1985). Symptoms and signs of pulmonary leukostasis include dyspnea, tachypnea, and hypoxemia without hypercapnia. Pulmonary leukostasis may result in diffuse capillary leakage or adult respiratory distress syndrome or mimic acute PE with ventilation-perfusion mismatches (Kaminsky et al. 2000). Pulse oximetry is more accurate than arterial pO_2 measurement in the assessment of oxygen saturation because WBCs consume oxygen in blood specimens obtained for analysis in test tubes. Neurologic signs and symptoms include vision-change headaches, dizziness, ataxia, stupor, confusion, and coma. Risk of intracranial hemorrhage is greatest after the leukocyte count decreases markedly, suggesting reperfusion injury as blood flow is restored to previously hypoxemic or ischemic capillary beds. Patients with leukostasis are often febrile owing to either inflammation associated with leukostasis or concurrent infection. Without treatment, the 1-week mortality rate is approximately 20–40 % (Bug et al. 2007). When both respiratory and neurologic status is compromised, the 1-week mortality rate reaches 90 % (Porcu et al. 1997).

The goal of treatment of leukostasis is to reduce the number of circulating leukocytes. Both chemotherapy and leukapheresis help rapidly reduce the number of circulating WBCs. However, only chemotherapy destroys leukemia cells in the bone marrow, which potentially improves survival. Systemic antileukemic therapy should be initiated early together with supportive care, such as adequate hydration, to reduce the risk of tumor lysis syndrome caused by rapid cell death. Alkalization of the urine and control of uric acid production using uricolytic agents (e.g., allopurinol, rasburicase) may be required to minimize the effects of urate nephropathy. Unnecessary blood cell transfusions should be avoided until the patient's blast count decreases, as they can increase blood viscosity and worsen symptoms.

Leukapheresis likely is most helpful in leukemia patients with WBC counts greater than 100×10^9/L, high percentages of blasts, and neurologic or pulmonary leukostasis manifestations. Under appropriate conditions, leukapheresis can potentially decrease the WBC count by 30–60 %, with improvement in symptoms. Leukapheresis is not recommended for patients with acute promyelocytic leukemia (APL) because it is usually not effective and can potentially worsen the intrinsic coagulopathy associated with APL.

Thrombocytosis

Thrombocytosis is defined as a platelet count greater than 500×10^9/L and can be classified as either reactive or primary. Reactive thrombosis is the more common form, usually caused by chronic inflammatory or infectious disorders, surgery, hypersplenism, asplenia, hemorrhage, iron deficiency, malignancy, or medications such as eltrombopag, romiplostim, vincristine, all-trans retinoic acid (ATRA), cytokines, and growth factors. Most patients with reactive thrombocytosis do not have any symptoms or need any treatment.

Symptomatic primary thrombocytosis occurs in patients with essential thrombocythemia and polycythemia vera, whereas patients with chronic myeloid leukemia or myelofibrosis who have thrombocytosis are likely asymptomatic. Patients may have both thrombotic and hemorrhagic episodes, yet the correlation between the extent of thrombocytosis and the risk of thrombosis is poor (Michiels et al. 2006). Symptoms and complications of thrombocytosis result primarily from microvascular and macrovascular thrombotic events. Microvascular symptoms include acroparesthesia and digital ischemia, erythromelalgia, peripheral gangrene, and ischemic neurologic symptoms. Macrovascular thrombosis can occur in the legs, renal artery, and coronary, pelvic, splenic, and hepatic veins. Hemorrhagic events occur in up to 40 % of patients, with the gastrointestinal tract as the primary site of bleeding complications (Michiels et al. 2006).

Thrombocytosis is rarely an emergency and does not always require treatment. However, in patients with marked primary thrombocytosis and acute thrombosis, emergent plateletpheresis may be useful to rapidly decrease platelet counts to below 400×10^9/L (Regev et al. 1997). However, this provides only temporary control of the platelet count. Cytoreductive therapy (e.g., anagrelide, hydroxyurea), which is reserved for high-risk patients (age greater than 60 years, history of thrombosis, or platelet count greater than 1500×10^9/L), is usually necessary (Pescatore and Lindley 2000; Harrison et al. 2005). Patients should also take aspirin, although this should be done with caution, as platelet function defects are not uncommon.

Anemia

Almost all cancer patients experience anemia at one point during their disease. Most cases of anemia in cancer patients can have several superimposed factors (Table 10.3). Although the list of its mechanisms is daunting, causes of anemia can be simplistically categorized as increased blood loss as in hemorrhage or hemolysis or as decreased blood production.

The spectrum of anemia at presentation is very broad, ranging from asymptomatic to severe depending on factors such as the underlying disease, patient's age and cardiopulmonary reserves, and anemia severity and acuteness. Common symptoms of anemia result from decreased oxygen delivery to tissues, including fatigue, weakness, headaches, dyspnea, palpitations, and dizziness. Patients may have worsening of

Table 10.3 Causes of anemia in cancer patients

I. Blood loss
A. Hemorrhage (see Acute Hemorrhage section and Table 10.8)
B. Hemolysis (peripheral destruction)
1. Intrinsic/inherited
a. RBC membrane: PNH, hereditary spherocytosis, hereditary elliptocytosis
b. Hemoglobinopathies: sickle cell anemia, thalassemia
c. Enzymes: G6PD deficiency, pyruvate kinase deficiency
2. Extrinsic/acquired
a. Immune-mediated
i. AIHA: warm and cold secondary to malignancies such as chronic lymphocytic leukemia, non-Hodgkin lymphoma, IgM gammopathy of unknown significance, solid tumors, and ovarian dermoid cysts
ii. Rheumatologic: SLE, ulcerative colitis, common variable immune deficiency, autoimmune lymphoproliferative disease, postallogeneic SCT, and organ transplantation
iii. Infections causing WAIHA: hepatitis C, A, and E and cytomegalovirus; infections causing CAIHA: mycoplasma and infectious mononucleosis
iv. ABO-incompatibility transfusion reaction
v. Drugs: sulfa, cephalosporins, quinidine, thiazides, NSAIDS, MTX, 5-FU, rifampin, ribavirin, sulfonylureas, and interferon-α
b. Mechanical hemolysis: hemolytic uremic syndrome, TTP, DIC, and hypersplenism
c. Infections and chemicals: malaria and hypotonic fluid
II. Decreased production of RBCs
A. Acute
1. Aplastic anemia
2. Acute leukemia
3. Overimposed infection: human parvovirus B19
4. Chemotherapy and radiation therapy
5. Myelophthisic anemia: primary myelofibrosis and metastatic solid tumors (breast, lung, and prostate cancer)
B. Chronic
1. Nutritional deficiency: iron, folate, and vitamin B_{12} deficiency (owing to increased RBC turnover)
2. Ineffective erythropoiesis, MTX, and poor intake
3. Resulting from underlying disease: hypoendocrine state (thyroid, adrenal, pituitary), uremia, chronic inflammation, liver disease

G6PD glucose-6-phosphate dehydrogenase, *AIHA* autoimmune hemolytic anemia, *SLE* systemic lupus erythematosus, *SCT* stem cell transplantation, *WAIHA* warm autoimmune hemolytic anemia, *CAIHA* cold autoimmune hemolytic anemia, *NSAIDs* nonsteroidal anti-inflammatory drugs, *MTX* methotrexate, *5-FU* 5-fluorouracil

symptoms of their pre-existing underlying diseases, such as coronary artery disease. Physical findings of anemia include pallor, tachycardia, and systolic ejection murmur. Syncope and hypotension can occur when acute anemia results from massive blood loss resulting in hypovolemia.

Evaluation of anemia begins with a careful history, physical examination with particular attention to symptoms and signs of acute bleeding, and laboratory tests (Table 10.4). A complete blood cell count, particularly mean corpuscular volume measurement, reticulocyte count, the reticulocyte production index or reticulocyte

Table 10.4 Evaluation of anemia

RBC indices
• Normal mean corpuscular volume and MCHC (normochromic, normocytic anemia) – Anemia of chronic disease – Hemolytic anemia – Anemia of acute hemorrhage – Aplastic anemia • Low mean corpuscular volume and low MCHC (hypochromic, microcytic anemia) – Iron deficiency anemia – Thalassemias • High mean corpuscular volume and normal MCHC (normochromic, macrocytic anemia) – Vitamin B_{12} deficiency – Folate deficiency
RI
• Calculation RI = (reticulocyte count × measured HCT/normal HCT)/maturation correction • Maturation correction For HCT: 36 % to 45 % → 1.0, 26–35 % → 1.5, 16–25 % → 2.0, and ≤15 % → 2.5 • Normal RI range is 1–3 %, with a mean of 2 %; indication of healthy bone marrow responding to acute blood loss
Suspected hemolytic anemia
• LDH measurement • Haptoglobin measurement • Indirect bilirubin measurement • DAT (Coombs test) • Urinalysis for hemoglobinuria
Suspected chronic conditions for anemia
• Ferritin measurement • Total iron-binding capacity measurement • Serum iron measurement • Vitamin B_{12} measurement • Folate and RBC folate measurement • Creatinine measurement • Thyroid-stimulating hormone measurement
Anticipation of treatment (also see Table 10.8)
• Type and cross for PRBCs • Platelets (pooled, apheresis, leukoreduction, irradiation, cytomegalovirus-negative, human leukocyte antigen matching, IgA-removed) • FFP • 4F-PCC • Cryoprecipitates • WBC transfusion

MCHC mean corpuscular hemoglobin concentration, *HCT* hematocrit

index (RI), and a peripheral blood smear provide the initial guidance in the differential diagnosis of anemia. The RI is reticulocyte count × (measured hematocrit/normal hematocrit)/maturation correction. An RI greater than 2 % suggests a healthy response of bone marrow to acute blood loss or hemolysis, whereas an RI less than 2 % suggests inadequate production of RBCs. A peripheral blood smear

Table 10.5 Evaluation of anemia: blood smears

I. Bone marrow infiltration (myelophthisis)
A. Leukoerythroblastic changes 1. Nucleated RBCs 2. Immature WBCs (e.g., myelocytes, metamyelocytes, occasionally myeloblasts) B. Teardrop forms C. Giant platelets
II. Hemolysis
A. Spherocytes B. Polychromasia
III. Mechanical hemolysis (DIC, TTP, prosthetic heart valve)
Schistocytes (RBC fragments)
IV. Iron deficiency anemia
A. Hypochromia (pale RBCs) B. Microcytosis (small RBCs) C. Poikilocytosis (variation in shape) D. Anisocytosis (variation in size) E. Pencil-shaped cells
V. Vitamin B_{12}/folate deficiency
A. Macro-ovalocytes (mean corpuscular volume > 115 fl) B. Anisocytosis C. Poikilocytosis D. Hypersegmented neutrophils
VI. Glucose-6-phosphate dehydrogenase deficiency
A. Heinz bodies (denatured hemoglobin) B. Bite and blister cells (from removal of Heinz bodies from the spleen)
VII. Renal failure (burr cells)
VIII. Liver disease (acanthocytes and target cells)

can identify morphologic abnormalities and cell inclusions (Table 10.5). Further evaluation will depend on suspected causes of anemia, including LDH, indirect bilirubin, and haptoglobin measurement; urinalysis for hemoglobinuria; a direct antiglobulin test (DAT; or Coombs test); and serum iron, ferritin, total iron-binding capacity, vitamin B_{12}, folate, RBC folate, creatinine, and thyroid-stimulating hormone measurement.

Management of anemia varies depending on the underlying cause, severity of symptoms, functional status, co-morbidities, and hemoglobin level. Typically, transfusion of PRBCs is required for symptomatic severe anemia or acute anemia with active bleeding in a patient with a hemoglobin level of 7–9 g/dL, although this threshold is controversial. At The University of Texas MD Anderson Cancer Center, a hemoglobin level of at least 9 g/dL is the goal for patients with leukemia. In patients with solid cancers without stem cell problems, recombinant human erythropoietin is administered to reduce the number of transfused PRBCs. The benefits of transfusion should be carefully weighed against its risks, such as transfusion reactions, anaphylaxis, volume overload, infection, and iron overload in cases with chronic transfusion.

Hemolytic Anemia

Hemolytic anemia, or peripheral destruction of RBCs, may be either inherited (intrinsic) or acquired (extrinsic). Inherited conditions lead to defects in (1) the RBC membrane, such as hereditary spherocytosis, hereditary elliptocytosis, and paroxysmal nocturnal hemoglobinuria (PNH); (2) hemoglobin, such as sickle cell anemia and thalassemia; and (3) enzymes, such as glucose-6-phosphate dehydrogenase deficiency and pyruvate kinase deficiency. Acquired and extrinsic causes of hemolytic anemia are classified as follows: (1) immune-mediated, as in (a) autoimmune (lupus, chronic lymphocytic leukemia, non-Hodgkin lymphoma, stem cell transplantation) and (b) drug-induced (acetaminophen, nonsteroidal anti-inflammatory drugs, sulfa drugs, rifampin, cephalosporins, ribavirin, quinidine, thiazide, methotrexate, 5-fluorouracil) anemia; (2) infectious (viral hepatitis, cytomegalovirus, mycoplasma, Epstein-Barr virus, human immunodeficiency virus); and (3) mechanical, such as (a) prosthetic heart valves, infection with malaria, spider and snake venom, and hemodialysis; and (b) microangiopathic hemolytic anemia and its causes of thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome, disseminated intravascular coagulation (DIC), pre-eclampsia, and eclampsia.

Diagnostic findings of hemolytic anemia include an RI greater than 2 %, elevated LDH level, elevated indirect bilirubinemia, hemoglobinuria, a low haptoglobin level, and observation of schistocytes or fragmented RBCs on peripheral blood smears. If an autoimmune cause of anemia is suspected, the DAT or Coombs test will be positive. Further testing for warm and cold agglutinin titers can specify warm and cold autoimmune hemolytic anemia, respectively.

The interaction of variables such as genetics, underlying cancer, drugs, infections, stress, diet, and comorbidities is complex and may lead to anemia in cancer patients. For example, glucose-6-phosphate deficiency is a sex-linked disease affecting mainly Mediterranean, West African, Middle Eastern, and Southeast Asian populations. Hemolysis in patients with it is precipitated by oxidant stressors such as infections, diabetic ketoacidosis, intake of fava beans, and administration of drugs such as sulfonamides, antimalarials, nitrofurans, phenacetin, synthetic vitamin K, naphthalene, and rasburicase, which is used to prevent tumor lysis syndrome. Old erythrocytes are affected by glucose-6-phosphate deficiency, making hemolytic crisis self-limiting. Peripheral blood smears demonstrate spherocytes, schistocytes, Heinz bodies, “bite” cells, and “blister” cells. Deficiency is diagnosed by measuring glucose-6-phosphate enzyme levels.

PNH is a clonal disorder with an abnormality in the gene involved in synthesis of the glycosylphosphatidylinositol anchor in the RBC membrane, which makes RBCs in patients with PNH susceptible to complement attacks. Hemolysis is exacerbated by any event that activates the complement system (e.g., infections, changes in plasma pH, hypoxemia, stress). Patients experience symptoms of anemia, such as fatigue, pallor or jaundice, hemoglobinuria, abdominal pain, and venous and arterial thrombosis, in unusual sites like the mesenteric and cerebral arteries. Treatment with eculizumab, which inhibits complement activation, is effective in preventing intravascular hemolysis.

Autoimmune hemolytic anemia comprises a heterogeneous group of diseases with respect to the type of antibody involved and the absence or presence of an underlying condition (Table 10.3). The DAT or Coombs test is used to detect antibodies and complement proteins bound to RBC surfaces. Autoimmune hemolytic anemia is further classified based on the temperature at which the antibody reacts with the RBC membrane and thus is called warm or cold antibody immune hemolytic anemia.

Mechanical hemolysis, such as microangiopathic hemolytic anemia, is a form of microcirculatory fragmentation by fibrin threads deposited in the arterioles. Common underlying causes of microangiopathic hemolytic anemia are malignant hypertension, pre-eclampsia, vasculitis, TTP, DIC, and vascular anomalies. The signs and symptoms of this type of anemia are those of intravascular hemolysis. Treatment is directed at the cause.

Decreased Production of RBCs

RBC production can be impaired by drugs, chemotherapy, radiation therapy, and infections affecting the bone marrow, resulting in aplastic anemia, pure red cell aplasia, myelophthisis, and myelofibrosis.

Aplastic anemia is rare but may have severe manifestations. Drug or chemical exposure is the cause in 50 % of cases. Viral hepatitis, radiation therapy, and pregnancy have been associated with aplastic anemia. Some patients are considered to have aplastic anemia of autoimmune origin.

The aplastic state may extend to all cell lines and results from destruction by immune-stimulated lymphocytes or marrow stem cell failure. Precise diagnosis necessitates bone marrow examination, but the causative factor may be difficult to determine. General treatment of aplastic anemia includes removal of suspected marrow toxins from the environment, avoidance of aspirin use, oral hygiene, and menses suppression. Transfusions are given under life-threatening circumstances only. Transplantation of bone marrow or peripheral blood stem cells from a histocompatible sibling can cure bone marrow failure, with reported survival rates of 77–90 %. Immunosuppression via use of antithymocyte globulin, antilymphocyte globulin, and cytotoxic chemotherapy is performed in the majority of patients who are not stem cell transplantation candidates. The severity of the disease varies widely, and the overall 5-year survival rate ranges from 30 % to 40 %. Bone marrow transplantation before blood product sensitization has resulted in an 80 % 5-year survival rate. This treatment is usually combined with immunosuppressive therapy consisting of use of antilymphocyte globulin. However, finding correct immunologic matches is difficult.

Pure red cell aplasia affects erythroid progenitors in the bone marrow but spares WBC precursors and megakaryocytes. It can be a consequence of cancer, most commonly thymoma, chronic lymphocytic leukemia, and large granular lymphocytic leukemia. The mechanism of pure red cell aplasia is immune-mediated via either

formation of autoimmune antibodies or T-cell–induced cytotoxicity. Parvovirus B19 infection should be considered in the differential diagnosis of pure red cell aplasia, particularly in susceptible patients with altered immunity. In addition to profound erythroid hypoplasia with erythroid maturation arrest, a characteristic bone marrow finding is giant pronormoblasts with prominent eosinophilic intranuclear viral inclusions. The treatment of choice is IV immunoglobulin.

Myelophthisic anemia is bone marrow failure resulting from replacement by an invading tumor, leukemia, lymphoma, or, rarely, granuloma. A more basic defect or inhibitor may complicate the problem because the degree of anemia cannot always be correlated with the extent of bone marrow invasion. Any patient with cancer may be subject to development of this type of anemia. Useful clues are signs of extramedullary hematopoiesis, such as hepatosplenomegaly and a leukoerythroblastic peripheral blood smear that demonstrates immature WBCs, nucleated RBCs, and poikilocytosis. Therapy is directed at the underlying disorder.

Myelofibrosis of unknown origin is the usual cause of primary bone marrow failure associated with extramedullary hematopoiesis. This myeloid metaplasia occurs in the liver and spleen and imparts a blood picture similar to that associated with myelophthisic anemia. Myelofibrosis may be diagnosed via bone marrow examination. Treatment is targeted therapy with a Janus kinase 2 inhibitor (e.g., ruxolitinib), splenectomy, or alkylating agents, which may be necessary to treat complications of extramedullary blood cell production, such as hepatosplenomegaly.

Other conditions in anemia cases associated with underproduction of RBCs are further categorized based on the mean corpuscular volume (Table 10.5). Additional chronic causes are hypothyroidism, hypoadrenalism, and hypopituitarism, resulting in a hypometabolic state in which the bone marrow responds poorly to treatment with erythropoietin. Anemia in patients with chronic renal failure is thought to be caused by a number of factors, including decreased erythropoietin production, hemolysis, suppression by dialyzable factors, and increased blood loss caused by platelet abnormalities, which combine to cause mild to moderate anemia. These chronic conditions can co-exist with acute causes of anemia in cancer patients.

Thrombocytopenia

Thrombocytopenia is defined as a platelet count less than 150×10^9/L. However, its pathologic effect of bleeding varies greatly according to platelet function and other pathophysiologic and clinical manifestations. The general consensus is that most patients with thrombocytopenia have no symptoms until the platelet count drops below 50×10^9/L. Bleeding can range from superficial in the mucosa and skin, such as petechiae, purpura, and ecchymoses, to critical, such as intracranial hemorrhage. Interestingly, thrombocytopenia does not always lead to bleeding but can instead lead to venous and/or arterial thrombosis, as in cases of heparin-induced thrombocytopenia (HIT). In patients with HIT, the rate of platelet reduction is important in

Table 10.6 Causes and evaluation of thrombocytopenia in cancer patients

I. Decreased bone marrow production
A. Chemotherapy, radiation therapy
B. Neoplastic bone marrow disease
1. Primary (leukemia, lymphoma, myelodysplasia)
2. Metastatic (breast, lung, prostate, colon, and stomach cancer)
C. Drugs: hydrochlorothiazides, antibiotics, alcohol
D. Infections
E. Nutritional deficiency
II. Increased peripheral destruction
A. Immune-mediated thrombocytopenia
1. Immune thrombocytopenia purpura
a. Primary/autoimmune
b. Secondary tumor and malignancy
i. Lymphoproliferative diseases: chronic lymphocytic leukemia, hemangioma
ii. Drugs: sulfa, heparin, quinidine, abciximab, vancomycin
iii. Rheumatology: SLE, antiphospholipid syndrome, vasculitis
iv. Infections: HIV, HCV, HSV, EBV, CMV, parvovirus, *Helicobacter pylori*
B. Non-immune
1. Microangiopathy hemolytic anemia: hemolytic uremic syndrome, TTP, DIC (from infection), pre-eclampsia, HELLP syndrome
2. Mechanical: cardiopulmonary bypass, hemodialysis
3. Drugs: cyclosporine, clopidogrel
II. Increased splenic sequestration
A. Neoplastic disease (lymphoma, myelofibrosis, leukemia)
B. Splenic vein obstruction (primary or metastatic liver disease, pancreatic cancer)
III. Evaluation
A. History and physical examination: drugs, bleeding symptoms and findings for hepatosplenomegaly, malignancy, infection, procedure exposure
B. Complete blood count, differentials, and peripheral blood smears (see Table 10.5)
C. Exclusion of pseudothrombocytopenia from clumping with ethylenediaminetetraacetic acid, so repeat sampling in a tube without anticoagulants

SLE systemic lupus erythematosus, *HIV* human immunodeficiency virus, *HCV* hepatitis C virus, *HSV* herpes simplex virus, *EBV* Epstein-Barr virus, *CMV* cytomegalovirus

recognizing the entity and need for early intervention. For example, a 50 % reduction in the platelet count from 400×10^9/L over 1–2 days results in an absolute count of 200×10^9/L, which appears to be normal. However, the rate of change in this setting and the timing of heparin exposure should prompt the clinician to be suspicious for HIT and respond accordingly.

Common etiologies of thrombocytopenia in the great majority of cancer patients are combinations of bone marrow pathologies and cancer treatments. Also, different cell lines are usually involved at some time. In summary, the causes of thrombocytopenia are decreased bone marrow production, accelerated peripheral destruction, and abnormal distribution. Suggested tests for evaluation of thrombocytopenia are listed in Table 10.6. Management of thrombocytopenia varies depending on the underlying biology. Similarly, use of prophylactic platelet transfusion is based on

several factors: absolute platelet count, platelet function, the patient's history and risk of bleeding, concurrent medical problems, and pending procedures.

Thrombocytopenia is an unavoidable outcome of chemotherapy and radiation therapy. It occurs most often in patients receiving intensive chemotherapy, particularly in the setting of hematologic malignancies and stem cell transplantation. It is typically observed 1–2 weeks after initiation of a treatment cycle. However, the platelet count nadir varies depending on the regimen. The severity of thrombocytopenia and its effect on specific megakaryocyte development also determines its timing and degree. Treatment with new agents such as bortezomib and lenalidomide also can contribute to thrombocytopenia. The most common intervention is to delay or reduce the dose of the next cycle to allow for bone marrow recovery. Platelet transfusion is the mainstay of supportive therapy. However, the feasibility of this transfusion should be considered owing to a shortage of platelets and the risks involved, including formation of alloantibodies, transfusion immune reactions, and infections. Another recent approach is the use of agents with thrombopoietic activity, such as cytokines and specific megakaryocyte growth factors. The only cytokine approved by the U.S. Food and Drug Administration, interleukin-11, may reduce the need for platelet transfusion. However, the toxicity profile for this cytokine, which has included edema (50 %), dyspnea, atrial arrhythmia, syncope, and fatigue, has precluded its use for routine supportive care.

Immune-mediated thrombocytopenia occurs most often in association with lymphoproliferative disorders. The prevalence is about 1–2 %, and it may occur at any time during the disease course. Immune-mediated thrombocytopenia associated with lymphoproliferative disorders has the same mechanism of platelet destruction as that of idiopathic immune thrombocytopenia. Standard treatment of primary idiopathic immune thrombocytopenia, which includes corticosteroids, IV immunoglobulin, anti-D antibodies, and splenectomy, is often successful but should focus on resolving the underlying disorder.

About two thirds of patients with myelodysplastic syndrome have thrombocytopenia. The cause of thrombocytopenia in myelodysplastic syndrome cases appears to be decreased platelet production as a result of accelerated megakaryocyte apoptosis. Treatment can be cumbersome because it can often cause thrombocytopenia. Management of thrombocytopenia in these cases is mainly supportive, including platelet transfusion, immunosuppression, immunomodulation, and use of thrombopoietic growth factors.

Thrombotic microangiopathy (TMA; manifesting as TTP or hemolytic uremic syndrome) is a well-described occurrence in cancer patients. It has two major pathophysiologic components: (1) stimulation of endothelial cells with the release of von Willebrand factor, leading to recruitment and activation of platelets with formation of thrombi in the microvasculature, and (2) deficiency or absence of ADAMTS-13, an enzyme in charge of proteolytic cleavage of von Willebrand factor. The pathogenesis of cancer-associated TMA has yet to be completely elucidated, but the most important factor likely is endothelial damage caused by endothelial toxicity of antineoplastic agents (mitomycin C, cisplatin, gemcitabine, and vascular endothelial

growth factor inhibitors) or directly related to the cancer or cancer-associated DIC. Severe thrombocytopenia occurs owing to recruitment of platelets in the microcapillaries. Also, acute anemia occurs owing to fragmentation of RBCs when passing though the fibrin mesh contained in the microthrombi. TMA is mostly seen in association with mucin-producing cancers (breast and stomach cancers) and in the setting of bone marrow or solid organ transplantation. Weakness, cough, dyspnea, fever, weight loss, bone pain, and abdominal pain are the most common presenting symptoms. Generally, biochemistry reveals markedly increased LDH levels, severe anemia, thrombocytopenia, and fragmented RBCs on peripheral blood smears. Treatment of the underlying neoplasia is the mainstay of therapy. Unlike in cases of idiopathic TTP, plasmapheresis and plasma infusion do not have roles in treatment of TMA caused by chemotherapy or transplantation. The prognosis for cancer-associated TMA is usually very poor.

HIT is a potentially catastrophic drug-mediated immune thrombocytopenia. It is most often associated with use of unfractionated heparin (1–4 %) but can also occur with that of other types of heparin, such as LMWHs. After several days of heparin exposure, antibodies against the PF4-heparin complex form. The IgG/heparin-PF4 complex then causes platelet activation via the platelet FcγIIa receptor. Thrombin is also activated in this process, resulting in a hypercoagulable state. Furthermore, HIT can cause both venous and arterial events, with high mortality rates. Diagnosis of HIT is basically clinical, with thrombosis and a decreasing platelet count (greater than 50 % drop from baseline) 5–10 days after initiation of heparin-based therapy. Antibodies can be detected using an enzyme-linked immunosorbent assay, although the specificity is poor. The gold standard of detection is the serotonin release assay, but it is used only in specialized laboratories. Management of HIT includes discontinuation of heparin, initiation of treatment with a direct thrombin inhibitor, and consideration of alternative anticoagulation strategies. The duration of risk for thromboembolism in patients with HIT is about 1 month. Once serology is negative for HIT, patients may be re-exposed to heparin.

Acute Hemorrhage

Overview

Cancer and its treatments promote bleeding owing to different systemic mechanisms that frequently exist concurrently. Common conditions are bone marrow suppression resulting from chemotherapy or biologic therapy; liver or renal failure resulting from tumor infiltration, use of drugs, or a comorbidity; and breach of the integrity of involved organs and blood vessels by surgery or radiation therapy. Causes of acute hemorrhage are listed in Table 10.7. Clinically, bleeding can be overt or occult, which manifests as anemia as in cases of colon carcinoma. If the hemorrhage is severe and urgent, simultaneous assessment and treatment may be necessary.

Table 10.7 Causes and treatments of hemorrhage in cancer patients

Vascular damage Malignancy Surgery Catheter	Treat underlying malignancy Consult surgery Removal or adjustment
Platelet Quantity: pseudothrombocytopenia (by EDTA) Thrombocytopenia Thrombocythemia Decreased production (e.g., bone marrow failure) Increased destruction Sequestration Qualitative: thrombocytopathies Drugs: aspirin Uremia Acquired von Willebrand disease	Repeat with a fresh specimen without anticoagulants Transfuse platelets Plateletpheresis Evaluate for cause and treat accordingly Treat cause of hypersplenism or splenectomy Discontinuation, platelet transfusion Dialysis, DDAVP, cryoprecipitates, estrogens DDAVP, IVIg, rFVIIa, immunosuppressants, plasmapheresis
Coagulation Deficiency of coagulation factors Vitamin K-dependent coagulation Factors II, V, VII, and X Warfarin, malnutrition, antibiotics Production impairment Liver malignancy Destruction Acquired factor inhibitors (e.g., factor VIII inhibitor)	Vitamin K IV or PO, 4F-PCC, FFP, rFVIIa Vitamin K, FFP, limited data for antifibrinolytics, estrogens, rFVIIa rFVIIa, FEIBA, immunosuppressants, plasmapheresis
Fibrinolysis Increased in APL DIC	ATRA, arsenic trioxide, platelets, cryoprecipitates Cryoprecipitates, platelets
Drugs Antiplatelet and anticoagulant	Discontinuation

EDTA ethylenediaminetetraacetic acid, *DDAVP* 1-deamino-8-D-arginine vasopressin, desmopressin, *IVIg* IV immunoglobulin, *rFVIIa* recombinant activated factor VII, *PO* by mouth, *FEIBA* factor eight inhibitor bypass activity (FEIBA VH anti-inhibitor coagulant complex)

Assessment

A comprehensive history helps identify the risk factors and contributing causes for acute hemorrhage, such as prior episodes of bleeding, use of antiplatelet agents or anticoagulants, concurrent liver or renal disease, and other comorbid conditions. Physical examination can further point to the source of defects in hemostasis. Mucosal and skin findings such as petechiae, ecchymosis, and immediate postprocedural bleeding suggest platelet abnormalities, whereas delayed bleeding after surgery or trauma, hematomas, and hemarthrosis may indicate coagulation defects.

Initial evaluation should begin with a complete blood count and determination of the PT, INR, and activated partial thromboplastin time (aPTT). For patients receiving

Table 10.8 Interpretation of abnormal coagulation tests

PT	aPTT	Differential
Prolonged	Normal	Factor VII deficiency (inherited, acquired, inhibitor), vitamin K deficiency (dependent factor II, V, VII, and X; warfarin, dietary, antibiotic), liver disease
Normal	Prolonged	Heparin; factor VIII (hemophilia A), IX (hemophilia B), XI, and XII deficiency; factor inhibitors; lupus anticoagulant; factor VIII; acquired von Willebrand factor
Prolonged	Prolonged	Heparin, warfarin, some DTIs; DIC; liver disease; factor II, V, IX, and/or X deficiency (inherited, acquired, inhibitor); hypofibrinogenemia or dysfibrinogenemia; massive transfusion

DTIs direct thrombin inhibitors

LMWHs such as enoxaparin and dalteparin, determination of the anti-Xa level rather than the PT or aPTT is required to assess their activities. Use of new anticoagulants, direct anti-Xa inhibitors such as rivaroxaban and apixaban, direct thrombin inhibitors, and dabigatran etexilate can only be monitored using special tests that are currently not routinely available. Again, patients' activities cannot be measured according to the PT or aPTT.

Prolonged PTs and INRs are common in patients who take the vitamin K inhibitor warfarin but less so in those with poor nutrition, who take antibiotics, who have liver disease, or, rarely, who have deficiency in or inhibition of factors VII, X, II, or V or fibrinogen. Prolongation of aPTT can be caused by treatment with heparin and deficiency in or inhibition of any of the clotting factors except factor VII. In a case with a prolonged aPTT, the thrombin time, which is the time required for conversion of fibrinogen to fibrin, can further characterize the defect in a patient with acute hemorrhage as one of the following: hypofibrinogenemia or dysfibrinogenemia, intentional or contaminating heparin, DIC, and paraprotein, which inhibits fibrin polymerization. To distinguish coagulation factor deficiency and inhibition in a case with a prolonged aPTT, mixing studies with 50 % normal plasma can correct the prolonged aPTT for coagulation factor deficiency but not inhibition. Subsequent measurement of the levels of the suspected factors or inhibitors can verify the abnormality. Similarly, prolonged aPTTs resulting from nonspecific inhibitors such as lupus anticoagulants cannot be corrected via mixing studies with 50 % normal plasma. However, lupus anticoagulation does not lead to bleeding but rather to venous and arterial thrombosis. Interpretation of coagulation results is shown in Table 10.8.

Additional coagulation tests include measurement of fibrinogen, fibrin degradation products, and D-dimer level for suspicion of DIC, liver disease, or thrombosis (low risk). If history and physical examination suggest the patient has a platelet abnormality despite having a normal platelet count, the physician should perform platelet function tests using a platelet function analyzer (PFA-100). For patients with near-normal hematocrits and platelet numbers, use of the PFA-100 has replaced analysis of the bleeding time because of improved sensitivity in identifying platelet dysfunction owing to aspirin use, von Willebrand factor, or other inherited or

acquired platelet dysfunction conditions. Platelet aggregation testing and von Willebrand factor antigen testing and activity can further define the defect responsible for acute hemorrhage.

Management

Treatment options for acute hemorrhage (Table 10.7) depend on the cause of bleeding: the coagulation and fibrinolysis cascades, the tissue integrity at the organ level, or both. A multidisciplinary collaboration among surgeons, medical specialists, and interventional radiologists is often required. General treatment modalities are reversal of antiplatelet (e.g., aspirin, clopidogrel, prasugrel) and anticoagulation (e.g., heparin, enoxaparin) treatment, correction of coagulopathy with coagulation factors (e.g., fresh frozen plasma [FFP], 4-factor prothrombin complex concentrate [4F-PCC], recombinant activated factor VIIa), inhibition of hyperfibrinolysis (e.g., aminocaproic acid [Amicar]), topical hemostatic agents, packing, ligation, radioablation, laser coagulation, and embolization. Risks and benefits must be considered when administration of coagulation factors or inhibition of fibrinolysis may tip the scale toward thrombosis or when an invasive procedure is involved, as manipulation of tissue may result in further bleeding. In patients with severe bleeding or hemodynamic instability, immediate resuscitation with fluid replacement and PRBC transfusion is required during ongoing evaluation. In some situations, correction of the hemostatic defect as the initial step may be sufficient to stop the bleeding. Based on the severity of the bleeding, a stepwise approach to management is recommended as described below.

Platelets can be transfused to correct severe thrombocytopenia or platelet dysfunction. Use of prophylactic platelet transfusion depends on the specific disorder; the clinical history, location, and severity of bleeding; and pending procedures. In general, the consensus at MD Anderson is to maintain a platelet count of at least 12,000/L in patients without excessive risks. For thrombocytopenia refractory to platelet transfusion, ongoing bleeding, platelet destruction, hypersplenism, and alloimmunization must be considered. These may necessitate further interventions, for example, slow platelet transfusion over 4 h, washing of platelets with vincristine, administration of low-dose vincristine, or transfusion of human leukocyte antigen-matched platelets.

To correct vitamin K deficiency (factor II, VII, IX, and X), the first-line intervention is to give vitamin K to enable the liver to produce the affected factors after treatment with warfarin at 5–20 mg via the oral or IV route. Full efficacy begins in 8–12 h. For emergent reversal of vitamin K antagonism, direct replacement of the factors can be performed using several products. Physicians have traditionally used FFP. However, FFP use requires time in preparation for blood type matching and infusion of a large volume. The recently developed and U.S. Food and Drug Administration-approved 4F-PCC is a new source of vitamin K-dependent coagulation factors shown to be as effective as FFP in urgent reversal of warfarin in patients

with major bleeding events according to clinical and laboratory measures (Sarode et al. 2013). A more recent study using 4F-PCC to reverse warfarin demonstrated superior effective hemostasis and rapid reduction of the INR with less volume overload than and equal adverse effects of FFP (Refaai et al. 2013). In extreme situations in which an additional hemostatic effect is necessary, recombinant activated factor VIIa can be added to FFP or 4F-PCC.

When bleeding occurs after a large transfusion of RBCs or evaluation time is limited, FFP can be given prophylactically. However, its use is limited because of the low concentration of coagulation factors in FFP in a large volume. A cryoprecipitate is preferred in patients with hypofibrinogenemia or dysfibrinogenemia because of its high concentrations of fibrinogen, von Willebrand factor, factor VIII, and factor XIII. Administration of specific clotting factors such as recombinant activated factor VIIa, factor VIII (for hemophilia A), factor IX (for hemophilia B), factor X, factor XIII, and von Willebrand factor is an effective treatment of deficiency in or inhibition of specific factors.

The following common treatments are used to correct coagulopathy owing to either factor deficiency or the presence of inhibitors: immunosuppressive agents such as corticosteroids, cyclophosphamide, rituximab, IV immunoglobulin, and plasmapheresis. Also, two unique coagulopathic entities can lead to acute hemorrhagic emergencies: DIC and APL.

DIC is an acquired syndrome characterized by exuberant systemic activation of coagulation and hypofibrinolysis. Deposition of fibrin-rich thrombi in the microvasculature and simultaneous bleeding owing to consumption of clotting factors contribute to further coagulopathy. The causes of DIC are solid and hematologic malignancies, sepsis, trauma, obstetric complications, and toxins. DIC can present in a spectrum of clinical manifestations: thrombosis to bleeding, insidious to acute, nonovert to overt, and asymptomatic to multiple organ failure. Diagnosing DIC can be a challenge because of its dynamic process and changing presentation at different levels of severity. Common laboratory findings are thrombocytopenia, prolonged PT and/or aPTT, elevated fibrin degradation product levels, and decreased fibrinogen levels. A more specific test is measurement of thrombin-antithrombin complex, which is a surrogate marker for generation of intravascular thrombin and consumption of anticoagulants (protein C, protein S, and antithrombin). Early recognition of the primary underlying condition is important to the initiation of immediate treatment of this condition and thus prevention of full DIC. Treatment of DIC is highly individualized, ranging from observation to aggressive transfusion of blood products. Although a consensus regarding specific targets is lacking, for high-risk patients such as those with APL or active bleeding, the following are judicious: platelet transfusion to 30,000–50,000/L, increasing the fibrinogen level to greater than 1 g/L with the use of a cryoprecipitate, and normalization of PT and PTT with the use of a cryoprecipitate and FFP. The role of anticoagulation with unfractionated heparin or LMWH is limited to cases of documented thrombosis or extensive microvasculature ischemia and infarcts.

A specific variation of DIC applies to patients with APL whose increased tissue factor and cancer procoagulant levels induce DIC. In addition, annexin II is produced

on the surface of APL cells, which enhances the conversion of plasminogen to plasmin via tissue plasminogen activator and hence drives coagulation toward hyperfibrinolysis instead of the predominant hypofibrinolysis. Despite improved prognosis for APL with administration of ATRA and arsenic trioxide, early death still occurs in up to 20 % of patients because of massive bleeding, with the preponderance occurring in the lung and brain. In cases of suspected APL-induced DIC, even before APL is definitively diagnosed, early induction therapy with ATRA and arsenic trioxide and replacement of platelet, fibrinogen, and clotting factors can reverse the coagulopathy (Menell et al. 1999).

Blood Transfusion Reactions

Transfusion of blood products is performed frequently and is important to management in cancer patients. The incidence of transfusion reactions varies with the type of product and reaction. The initial clinical presentation of a reaction can be a challenge to a clinician because the early symptoms for the two most common benign conditions—febrile nonhemolytic transfusion reactions and allergic transfusion reactions—are indistinguishable from those of the rarer life-threatening conditions, such as acute hemolytic transfusion reactions and transfusion-related acute lung injury (TRALI). Furthermore, development of hemolytic transfusion reactions can be delayed for up to 2 weeks when the clinician determines that the event could be out of the normal temporal association. Typically, the initial symptoms of blood transfusion reactions are fever, chills, rigor, nausea and vomiting, tachycardia, and hypotension, which may develop during or several hours after transfusion. Early management should include stopping the transfusion, maintaining the transfused blood product for further testing, stabilizing the patient with antipyretic administration and fluid resuscitation, tests for cross-matching, plasma-free hemoglobin measurement, the DAT (Coombs test), and immediately notifying the blood bank. A common dilemma is administration of premedication for transfusion. Multiple studies, including a prospective, randomized, double-blind controlled trial of acetaminophen and diphenhydramine versus placebo, did not demonstrate decreases in transfusion reactions but did demonstrate that giving leukoreduced blood products reduced the risk of febrile nonhemolytic transfusion reactions (Kennedy et al. 2008).

Four common and potentially fatal blood transfusion reactions (Table 10.9) are discussed in more detail below.

Acute Hemolytic Transfusion Reactions

Acute hemolytic transfusion reactions are usually caused by mistakes in blood group typing or confusion in matching the blood unit with the patient during the transfusion chain. Incompatible donor RBCs are rapidly destroyed by preformed

Table 10.9 Transfusion reactions

Immunologic
1. Febrile nonhemolytic transfusion reaction 0–6 h after transfusion
2. Allergic transfusion reaction
3. Acute hemolytic transfusion reaction less than 24 h after transfusion
4. Delayed hemolytic transfusion reaction days to 2 weeks after transfusion
5. Other types of hemolytic reactions (e.g., minor incompatibility)
6. Posttransfusion purpura: alloantibody-mediated thrombocytopenia after RBC transfusion with innocent bystander effect
7. TRALI
8. Transfusion-associated graft-versus-host disease
Nonimmunologic
1. Transfusion-associated circulatory overload
2. Citrate reaction
3. Hemosiderosis
4. Embolism (air or detritus)
Transfusion-transmitted infections
1. Transmission via blood Bacteria, viruses, protozoa, helminths, prions
2. Transmission via plasma derivatives Parvovirus, HAV, HBV, HCV, and HIV (extremely rare, only when pathogen inactivation fails)

HAV hepatitis A virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus

recipient antibodies, usually anti-A or anti-B antibodies, which bind to the corresponding antigens and activate the complement cascade, leading to direct intravascular hemolysis. Acute ABO-incompatible transfusion hemolytic reactions also cause transfusion-related death.

Common symptoms and signs of acute hemolytic transfusion reactions are fever, chills, nausea, dyspnea, chest pain, and back or flank pain, which may occur shortly after the transfusion is started and with transfusion of as little as 10–15 mL. Complement-mediated rapid intravascular hemolysis may lead to DIC, shock, and acute renal failure with transfusion of a large amount of mismatched blood.

Diagnosis of acute hemolytic transfusion reactions requires testing of pretransfusion and posttransfusion blood specimens and revision of all documents associated with the transfusion. A DAT facilitates detection of immunoglobulins (IgG, IgA, and IgM) and/or complement factors (C3c and C3d) in RBCs of patients with monovalent antisera. Other tests include peripheral blood smears (to look for schistocytes) and bilirubin, haptoglobin, LDH, and urine hemosiderin measurement.

Besides stopping the transfusion immediately, management of acute hemolytic transfusion reactions consists of fluid resuscitation, airway protection, and tissue perfusion maintenance. Mannitol and furosemide can be used as necessary to maintain urine output and minimize renal injury. Death occurs in approximately 1 of 30 patients who receive ABO-incompatible RBCs. Prevention of ABO-incompatible transfusions is the optimal strategy.

Unlike with ABO-mediated hemolytic transfusion reactions, hemolytic transfusion reactions are usually delayed with the use of antibodies against non-ABO RBC

antigens, such as Rh (c and E), Kidd, Duffy, and Kell. These reactions occur days to weeks after transfusion, usually cause extravascular hemolysis owing to non-complement-binding antibodies coating the donor RBCs, and are characterized by fever, mild anemia, and/or hyperbilirubinemia. Laboratory findings include spherocytosis on blood smears, a new positive DAT (Coombs test), and a new positive antibody screen. Treatment of hemolytic transfusion reactions is rarely required and mainly supportive.

TRALI

TRALI is the most frequent and most dangerous transfusion reaction and can be caused by use of any blood product, including whole blood, PRBCs, platelet products, FFP, cryoprecipitates, IV immunoglobulin, and stem cell preparations. The precise mechanism that leads to TRALI is not known, but insults to the alveolar microcapillaries that lead to increased permeability are observed.

A specific test for TRALI is lacking, and the clinical picture of TRALI is very similar to other forms of acute respiratory distress, such as congestive heart failure. The possibility of TRALI should always be considered in assessing a patient who is being transfused and experiences acute respiratory distress. The classical presentation of this reaction includes acute onset of respiratory distress during or within 6 h after transfusion, hypoxemia, and bilateral infiltrations on chest X-rays. Other signs and symptoms of TRALI include frothy sputum, fever, and hypertension or hypotension.

When TRALI is suspected, the transfusion should be stopped immediately. A complete blood count with differential and chest radiography should be performed. If the patient is intubated, undiluted edematous fluid in the lungs and plasma can be obtained simultaneously as soon as possible for determination of total protein concentrations. A high protein ratio (greater than 0.6) between lung fluid and plasma would suggest increased capillary leakage rather than cardiac hydrostatic pulmonary edema.

Management of TRALI is often supportive, including oxygen supplementation with or without mechanical ventilation and fluid management with avoidance of diuretics, as pulmonary edema associated with this condition is noncardiogenic, and the patient is often hypovolemic owing to extravasation of fluid into the lungs. About 80 % of TRALI cases resolve within 96 h, whereas fatal reactions occur in about 10 % of cases.

Bacterial Contamination

Bacterial contamination of transfused blood products is the third leading cause of transfusion-associated deaths. The risk is higher with platelets than with RBCs because the storage of platelets at room temperature permits the survival and rapid

proliferation of bacteria among them. Contamination may occur during blood collection or processing, via contaminated equipment, or by transfusion of blood obtained from a donor with asymptomatic bacteremia. The spectrum of bacteria reported to contaminate blood and blood components is broad. The most frequent sources of contamination are skin flora, with the most common species being *Staphylococcus aureus* and *Staphylococcus epidermidis*. Researchers have identified a small number of enteric or environmental flora in platelets. Most deaths associated with RBC or platelet transfusions are caused by infection with gram-negative organisms.

Patients who receive contaminated blood products can experience rigor, fever, tachycardia, nausea, vomiting, shortness of breath, and decreased blood pressure. Also, bacterial sepsis can develop and be catastrophic. In such cases, the transfusion should be stopped immediately, and the remaining blood product should be investigated for contamination and other causes of transfusion reactions. Blood cultures should be performed, and treatment with IV broad-spectrum antibiotics should be started immediately, especially if the patient is immunocompromised. The choice of antibiotics will be determined by local resistance patterns. Strategies for reducing the risk of sepsis resulting from blood product contamination include avoidance of unnecessary transfusions; optimization of blood collection, processing, and storage procedures; and implementation of tests to detect the presence of bacteria in blood products.

Severe Allergic (Anaphylactic) Reactions

Anaphylactic or anaphylactoid reactions may occur within seconds or minutes following the initiation of a transfusion of blood plasma, RBCs, platelets, granulocytes, a cryoprecipitate, or gamma globulin. The highest incidence is found with platelet transfusion followed by plasma transfusion. Allergic reactions usually occur in patients with IgA deficiency who have anti-IgA antibodies. In these patients, pre-existing anti-IgA antibodies react with IgA in transfused blood products, leading to immediate hypersensitivity responses. Allergic reactions can be caused by other serum proteins and blood product components, such as platelet-derived microparticles, or by drugs or chemicals administered before or during the transfusion.

A complete history of allergic reactions to any medications, biologic materials such as blood products and proteins, and food products is an essential part of any complete history for a patient having allergic reactions. Identification of a patient at risk prior to transfusion may prevent a catastrophic anaphylactic event. Depending on the allergy, premedication may attenuate or prevent an allergic event.

Anaphylactic reactions are generalized in nature and have multiple organ system involvement, manifesting predominantly as cardiovascular instability and respiratory distress. Symptoms can include flushing, hives with or without itching, angioedema with associated stridor, generalized wheezing, shortness of breath, coughing,

vomiting, diarrhea, and cardiovascular collapse with shock syndrome. A very rapid onset is characteristic of transfusion anaphylaxis, manifesting as hypotension, shock, angioedema, and respiratory distress within a few seconds to a few minutes after exposure to the inciting agent or agents, although it can occur within 1 h after exposure. Shock and vascular collapse must be differentiated from other causes of these reactions, such as sepsis, heart failure, hemolytic transfusion reactions, and vasovagal events. Furthermore, acute respiratory decomposition must be differentiated from a sudden severe asthma attack, pulmonary embolus, or angioedema. In cases of both vascular and respiratory failure, skin findings such as flushing, hives, and itching are highly suggestive of anaphylaxis syndrome. However, some patients with transfusion anaphylaxis have no skin findings.

Anaphylaxis is a medical emergency, and immediate treatment is required for the patient to survive it. Upon detection and diagnosis of an allergic reaction, the transfusion must be stopped immediately and not be restarted. The patient should receive appropriate airway management and additional supportive care, such as oxygen and IV fluids. Simultaneously, 0.3–0.5 mg of epinephrine (1-mg/mL preparation) should be given intramuscularly and repeated every 3–5 min as needed. Patients receiving β-blockers who may not have responses to treatment with epinephrine can be given 1–2 mg of IV glucagon over 5 min followed by infusion at 5–15 μg/min. Antihistamines, glucocorticoids, bronchodilators, and other vasopressors can be given, if necessary. Most cases will resolve within hours after initiation of proper treatment, but as many as 20 % of patients may have a biphasic course or relapse within hours after treatment. Patients with refractory anaphylaxis should be admitted to the intensive care unit.

Patients who have experienced transfusion-induced anaphylaxis but continue to have blood replacement needs may benefit from pretransfusion measurement of IgA levels and anti-IgA antibodies, especially IgE-type anti-IgA antibodies, if available, in serum. Use of IgA-deficient blood components for future transfusion is recommended for patients who are IgA-deficient but have circulating anti-IgA antibodies. If a patient does not have circulating IgA but has had an anaphylactic reaction to transfusion of unwashed blood components, use of washed blood components for future transfusion is recommended.

Key Practice Points

- Cancer patients have markedly increased risk of VTE, and accurate diagnosis relies on pretest probability and objective confirmation. LMWHs are the preferred therapeutic agents.
- IVC filters are indicated when anticoagulation is absolutely contraindicated or has failed. Until the safety of a temporary IVC filter for permanent placement is proven, it should be removed as soon as anticoagulation can be started. Otherwise, a permanent IVC filter should be used for indefinite PE secondary prophylaxis.

- Hyperviscosity caused by increased immunoglobulin levels in serum or increased numbers of cellular blood components can impede capillary blood flow, leading to ischemia and organ dysfunction.
- Plasmapheresis is the treatment of choice for acute severe HVS caused by paraproteinemia, but treatment of the underlying etiology should be initiated as soon as possible to affect the disease process or improve survival.
- Management of anemia varies depending on the underlying cause, severity of symptoms, functional status, and comorbidities as well as hemoglobin level.
- Thrombocytopenia in cancer patients is multifactorial and often related to the cancer and its treatment.
- Treatment of acute hemorrhage may vary with the mechanism and source of the bleeding. Simultaneous assessment and treatment may be necessary.
- Hemostatic defects should be corrected promptly. New antiplatelet agents, anticoagulants, and antidotes are available.
- Transfusion reactions should always be considered when a patient becomes symptomatic hours to 2 weeks after transfusion of blood products.
- Transfusion should be stopped immediately and an evaluation should be carried out to rule out an acute hemolytic anemia reaction and clerical error for a patient with symptoms of a blood transfusion reaction.

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Chapter 11
Chemotherapy-Related Emergencies

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Contents

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Chapter Overview

Chemotherapy and other cytotoxic therapies, such as monoclonal antibody-based and targeted therapies, have played a significant role in the survival of cancer patients. Despite its usefulness, chemotherapy may lead to significant adverse events owing to side effects and to hypersensitivity and infusion-related reactions. Monitoring protocols and education of both health care professionals and patients about potential side effects and adverse reactions are key to early recognition and management of these events. Premedication regimens should be considered for use with chemotherapeutic and cytotoxic agents with a high likelihood of causing hypersensitivity reactions. Desensitization protocols also may be required, and medications needed for treatment of these reactions should be made readily available. Another potential source of morbidity during treatment is the fact that many cytotoxic agents are vesicants or vascular irritants. Symptoms of vascular irritation can appear immediately but are not permanent, whereas vesication can cause necrosis and permanent local injury, and use of antidotes may be necessary. Creation and use of institutional guidelines, order sets, and policies can be very helpful in preventing extravasation and optimizing outcomes in patients who receive chemotherapy or other cytotoxic therapies.

Introduction

Despite the increasing incidence of cancer, with an estimated 1,660,290 new cases in 2013, the 5-year relative survival rate for cancer has improved greatly over the past 20 years, going from 49 % in 1975–1977 to 66 % in 2004–2010 (Howlader et al. 2014). Chemotherapy and use of cytotoxic agents such as monoclonal antibodies and targeted therapeutics have played a significant role in this improvement. Furthermore, the National Cancer Institute estimated that the number of cancer survivors on January 1, 2012, was about 13.7 million (Cancer Facts & Figures 2013). Notwithstanding its usefulness, chemotherapy may lead to significant adverse events owing to hypersensitivity to it, infusion-related reactions, and side effects. Monitoring protocols and education of both health care professionals and patients about the potential side effects of and adverse reactions to chemotherapy are key to early recognition and management of these events. Also, creation and use of institutional guidelines, order sets, and policies can be very helpful in preventing and managing drug extravasation and optimizing outcomes in patients who receive chemotherapy. In this chapter, we provide an overview of the most significant immediate and short-term effects of chemotherapy and other cytotoxic therapies, with a focus on the multidisciplinary diagnostic and management strategies currently used at our institution.

Hypersensitivity Reactions

Hypersensitivity is one of the most common types of immediate reactions to chemotherapy. In our ambulatory chemotherapy unit, hypersensitivity occurs in about 0.31 % of chemotherapy infusions (256 of 81,580 infusions in 2004) (Escalante et al. 2006). Taxanes, L-asparaginase, epipodophyllotoxins, and platinum-based compounds are suggested to have much higher propensity for causing hypersensitivity reactions than other agents (Kingsley 2008). Seventy-three percent of the reactions described above took place during the first 2 cycles of therapy. However, the cycles varied markedly according to chemotherapeutic agent (cycles 1–14) (Escalante et al. 2006). Risk factors for hypersensitivity reactions include allergies to other medications, history of atopy, and prior exposure to the same chemotherapeutic agent (Allen 1993).

Clinical Manifestations

The most common organ systems involved in hypersensitivity reactions are the cutaneous, gastrointestinal, pulmonary, and cardiovascular systems (Atkinson and Kaliner 1992). The most common symptoms and signs reported in our institution have been flushing, dyspnea, chest discomfort, pruritus, elevated blood pressure, back pain, chills, hypoxia, nausea, tachycardia, hypotension, fever, and abdominal discomfort (Table 11.1). However, the symptoms and signs of hypersensitivity reactions may vary significantly according to chemotherapeutic agent.

Table 11.1 Most common symptoms of hypersensitivity reactions

Symptom/sign	Incidence rate
Overall severity	
Mild	58.2 %
Moderate	32.8 %
Severe	9.0 %
Flushing	54.7 %
Dyspnea	29.7 %
Chest discomfort	26.2 %
Pruritus	24.6 %
Elevated blood pressure	19.5 %
Back pain	16.8 %
Chills	15.6 %
Hypoxia	14.8 %
Nausea	14.1 %
Tachycardia	11.7 %
Hypotension	10.9 %

Taxanes

Paclitaxel has the highest rate of hypersensitivity reactions among all taxanes, as up to 30 % of patients may experience major reactions without premedication (Levett et al. 2002). Major risk factors for hypersensitivity seem to be a fast infusion rate and short infusion schedule. Researchers have debated that a reason for the increased incidence of these reactions is that paclitaxel is insoluble and requires use of the solvent polyethoxylated castor oil (Kolliphor EL [formerly Cremophor EL]) for administration, which increases its toxicity and incidence of hypersensitivity episodes and entraps paclitaxel in micelles, decreasing its availability to tumor cells (Zhang et al. 2005; Weiss et al. 1990). In an attempt to reduce these effects, investigators have examined new paclitaxel formulations. One of these novel formulations that received U.S. Food and Drug Administration approval is nanoparticle albumin-bound paclitaxel (Abraxane). In a study of 175 patients, authors reported no Abraxane dose interruptions owing to hypersensitivity reactions (Socinski et al. 2010).

Most hypersensitivity reactions to taxanes occur within 2–10 min after the infusion starts and tend to improve within 15–30 min, and same-day rechallenge after improvement of symptoms usually does not lead to recurrence of the reactions. Minor reactions are much more common than major ones and include flushing, chest tightness, back pain, pruritus, and erythematous rash. Major hypersensitivity reactions include dyspnea, bronchospasm, hypotension, urticaria, and angioedema. We recommend premedication with steroids and antihistamines (H_1 antagonists and H_2 blockers) to reduce the incidence of major hypersensitivity reactions (1–3 %) (Levett et al. 2002).

Platinum-Based Agents

Although hypersensitivity reactions to carboplatin are less common than those to cisplatin, widespread use of the former agent for many different cancers makes these reactions a significant concern in ambulatory chemotherapy units. All platinum-based compounds cause type I reactions that seem to be mediated by IgE, and cross-reactivity among platinum analogs is possible. Cisplatin can cause hypersensitivity reactions in up to 20 % of patients. Furthermore, it may cause type II reactions. Anaphylaxis may occur in up to 5 % of patients without premedication. Oxaliplatin has caused hypersensitivity reactions in up to 12 % of infusions without premedication (Meyer et al. 2002). The most common symptoms of hypersensitivity reactions to these agents are rash (including urticaria), bronchospasm, and hypotension, but unlike with taxanes, reactions to platinum-based compounds can be very severe and even fatal if not treated aggressively.

Asparaginase

Hypersensitivity reactions to L-asparaginase usually occur after administration of the second dose, and the reaction risk increases with each subsequent dose, with rates of up to 33 % by the fourth cycle (Levett et al. 2002). Fortunately, anaphylaxis

is not common (less than 10 % of cases), and fatal reactions are even rarer (less than 1 % of cases). New formulations such as pegylated asparaginase are covalently attached to polyethylene glycol and do not appear to cause anaphylactic reactions. In addition to the risk factors described above, use of high doses (more than 6000 IU/m^2/day) and intravenous administration increase the risk of hypersensitivity reactions to asparaginase. Common symptoms of hypersensitivity to asparaginase include pruritus, dyspnea, agitation, rash/urticaria, angioedema, hypotension, laryngospasm/bronchospasm, nasal congestion, and pain. These are typically type I reactions and usually occur within 1 h after administration.

Alkylating Agents

The most commonly used classical alkylating agents are cyclophosphamide and ifosfamide, which cause type I reactions. However, the etiology of these reactions is unclear, as mesna, given together with ifosfamide, by itself can also cause type I reactions. Common symptoms include rash/urticaria, angioedema, and anaphylaxis. Chlorambucil and melphalan also cause type I hypersensitivity reactions, but they are rare unless melphalan is given intravenously (2–4 %). Chlorambucil can cause hemolysis, toxic epidermal necrolysis, and pneumonitis, and melphalan usually causes urticaria and angioedema (Levett et al. 2002). Procarbazine and dacarbazine are considered by most researchers to be nonclassical alkylating agents. Procarbazine can cause both type I and type III hypersensitivity reactions in up to 18 % of patients. The most common symptoms of type I reactions are urticaria and maculopapular rash, whereas that of type III reactions is allergic alveolitis.

Anthracyclines

Authors have not reported any hypersensitivity reactions to idarubicin, but daunorubicin and doxorubicin can cause type I reactions. Pruritus, erythematous rash, urticaria, hypotension, and anaphylaxis are common symptoms, but cross-reactivity seems to be uncommon.

Antimetabolites

IgE-mediated hypersensitivity reactions to cytarabine are rare, with symptoms including chest pain, dyspnea, angioedema, urticaria, fever, and hypotension. Another potential reaction to administration of this drug is cytarabine syndrome (neutrophilic eccrine hidradenitis and palmar-plantar erythema). Intrathecal administration of liposomal cytarabine has not been associated with any hypersensitivity reactions (Benesch et al. 2009). Because 6-mercaptopurine and its imidazole analog azathioprine are used more frequently for conditions such as arthritis and inflammatory bowel disease than for cancer, most data on hypersensitivity reactions to it are

derived from studies of the former conditions. Furthermore, concurrent use of steroids is common in the treatment of these conditions and may have influenced the reaction rates reported in the literature. The rate of hypersensitivity reactions (excluding pancreatitis) for 6-mercaptopurine was 2.7 % in a large series, with the most common symptoms being fever, arthralgia, and back pain (Korelitz et al. 1999). Most patients will have recurrence of these hypersensitivity reactions during rechallenge, and cross-reactivity with azathioprine is expected. Common symptoms of hypersensitivity reactions to azathioprine include fever, urticaria, rash, arthralgia, and dyspnea. Fortunately, hypotension and distributive shock occur very infrequently. The mechanism of these reactions is unknown, but investigators believe that these agents or their metabolites may function as haptens and bind to protein molecules to induce type I hypersensitivity reactions.

Topoisomerase Inhibitors

Hypersensitivity reactions to topoisomerase inhibitors are more common in children than in adults, more common for teniposide than for etoposide (7 % versus 3 %), and more common when given intravenously (etoposide) than via other routes. These can be type I (urticaria, angioedema, bronchospasm, hypotension, flushing, and rash) or type II (particularly hemolytic anemia with teniposide) reactions. However, etoposide is insoluble, requiring the use of solvents such as benzyl alcohol, Kolliphor EL, and polysorbate 80 (Tween 80), which by themselves may play a role in causing hypersensitivity reactions. The symptoms of these reactions can occur during administration of the first dose and within the first 10 min after infusion. Patients should not undergo rechallenge if these symptoms are severe or slow to resolve.

Miscellaneous Chemotherapy

Methotrexate can cause both type I (rash, urticaria, pruritus, angioedema, and hypotension) and type III (pneumonitis, pleural effusions, lung eosinophilia, hilar adenopathy, and cutaneous vasculitis) hypersensitivity reactions. Mitomycin C can cause delayed type IV reactions when given intravesically in up to 10 % of patients. Symptoms include erythematous, vesicular, and pruritic rash and angioedema. Skin reactions can be useful in predicting hypersensitivity reactions. Fluorouracil rarely causes type I reactions, consisting of angioedema and hypotension. In addition, bleomycin rarely causes fatal reactions but usually causes urticaria, bronchospasm, and periorbital edema. Use of a test dose of 1 mg of bleomycin is recommended. Mitoxantrone can cause erythematous rash and angioedema, and rechallenge can cause reaction recurrence (Levett et al. 2002).

Management Algorithm

The keys to optimal management of hypersensitivity reactions are prophylaxis, clinical staff training and patient education on potential symptoms of the reactions to shorten time to treatment, and desensitization, if recommended. For high-risk chemotherapeutic agents, prophylaxis can be administered with premedication in the form of 20 mg of dexamethasone, 50 mg of diphenhydramine, or 300 mg of cimetidine (or other H_2 blockers). The typical desensitization regimen for paclitaxel consists of 20 mg of dexamethasone given orally every 6 h for 4 doses followed by the prophylactic regimen described above.

Figure 11.1 shows the algorithm used in our institution for treatment of hypersensitivity reactions. It comprises management recommendations that should be adapted to each patient's diagnosis and comorbid conditions. The first step in the algorithm is to monitor the patient for any signs or symptoms of hypersensitivity and stop the infusion if any are detected. If the patient is unresponsive, a "code" should be called, and his or her vital signs should be monitored every 5 min. If fever, chills, and/or rigor develop, 1000 mg of acetaminophen should be given unless the patient is a stem cell transplant recipient or has received acetaminophen within the last 4 h. If chills persist, administration of a low dose of meperidine should be considered. Patients also should be monitored for signs of hypoxia, with oxygen supplementation given as needed. If the patient experiences flushing, pruritus, rash, or hives, 50 mg of diphenhydramine should be given intravenously over 2 min.

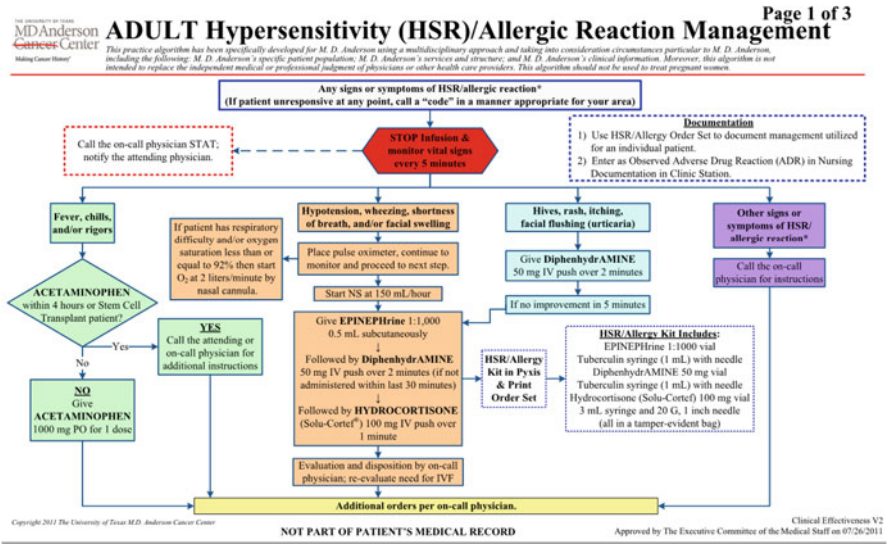

Fig. 11.1 Algorithm used at MD Anderson for treatment of hypersensitivity reactions. *NS* normal saline, *IV* intravenous, *IVF* intravenous fluid

For more severe symptoms such as hypotension, shortness of breath with wheezing or stridor, and swelling of the face, lip, or tongue, the following should be given: (1) normal saline at 150 mL/h, (2) 0.5 mL of epinephrine (1:1000) subcutaneously, (3) 50 mg of diphenhydramine intravenously over 2 min, and (4) 100 mg of hydrocortisone intravenously over 1 min. Patients who have reactions to paclitaxel (diluted in Kolliphor EL) usually have good prognoses despite frequently presenting with severe symptoms. These patients typically present with flushing, chest and/or back tightness, hypoxia, shortness of breath without stridor or wheezing, and hypertension or hypotension, and they should be given 50 mg of diphenhydramine and 100 mg of hydrocortisone, only adding epinephrine if their symptoms worsen or do not improve within 15–30 min after discontinuation of the infusion. In our institution, only 3.2 % of patients with hypersensitivity reactions have been transferred to our emergency center, 2.0 % have been admitted to the hospital, 84.0 % have undergone rechallenge the same day (88.1 % with no further reactions), and 94.8 % have been discharged.

Systemic Reactions to Monoclonal Antibodies

Administration of monoclonal antibodies frequently may lead to massive release of cytokines. The most common symptoms of systemic reactions to these antibodies are fever and rigor. Occasionally, they may lead to dyspnea, hypoxia, hypotension, and, rarely, death. The treatment of these reactions is similar to that of hypersensitivity reactions to chemotherapeutic agents. Systemic symptoms specific to individual agents are described below.

Denileukin Diftitox

Denileukin diftitox works by binding to the interleukin-2 receptor and delivering diphtheria toxin to lymphoma cells, inhibiting cellular protein synthesis and leading to cell death. Severe reactions to denileukin diftitox occur in 2 % of patients and consist of rash, dysphagia, back pain, shortness of breath, tachycardia, chest pain, vasodilatation, and syncope (Levett et al. 2002). The treatment of these reactions is similar to that of hypersensitivity reactions and includes discontinuation of the drug and intravenous administration of antihistamines, hydrocortisone, and epinephrine as necessary.

Another significant reaction to the use of denileukin diftitox is capillary (vascular) leak syndrome. Its symptoms, which usually occur within 2 weeks after infusion, consist of vascular leakage, hypoalbuminemia, severe edema, pleural effusion, and hypotension. Only supportive care for it is necessary, which may include intravenous fluids, diuretics, and albumin infusion. Further infusions of denileukin diftitox should be delayed until the patient's albumin level is greater than 3.0 g/dL, if possible. Premedication with corticosteroids is recommended.

Trastuzumab

The HER-2 proto-oncogene is overexpressed in up to 35 % of breast cancer cases. Trastuzumab is a humanized monoclonal antibody against HER-2/neu (c-erb B2) protein that is frequently used in the treatment of metastatic breast cancer. Fever and chills are the most common symptoms of reactions to trastuzumab during the first infusion; other effects include nausea, vomiting, diarrhea, severe myalgia, and pain at the tumor site (Ewer et al. 2005). Supportive treatment, including acetaminophen, opiates (e.g., meperidine), antiemetics, and antidiarrheals, should be considered.

Rituximab

Used commonly in the treatment of lymphomas, leukemias, and some rheumatologic conditions, rituximab is a humanized murine monoclonal antibody directed against CD-20, a B-cell-specific surface molecule. Reactions to rituximab are very common and have occurred in up to 84 % of patients in some trials (Oldham 1983). Most symptoms of these reactions usually occur 30–120 min after the first infusion and are mild, including transient fever, chills, headache, nausea, and fatigue. Premedication regimens often include diphenhydramine and acetaminophen to ameliorate the symptoms. If reactions occur, the infusion of rituximab should be interrupted and then restarted at half the initial infusion rate once the symptoms resolve. Supportive treatment is recommended, and most symptoms resolve with interruption or slowing of the infusion. Serious effects of reactions to treatment with rituximab may be related to immune response to the use of a humanized murine antibody and include pain at the tumor site, bronchospasm, arrhythmias, hypotension, rash, and even angioedema. The treatment of these symptoms is similar to that of hypersensitivity reactions and includes discontinuation of the drug and intravenous administration of antihistamines, hydrocortisone, and epinephrine as necessary.

Gemtuzumab Ozogamicin

Used in the treatment of acute myeloid leukemia, usually when the patient may not be able to tolerate more cytotoxic chemotherapy, gemtuzumab ozogamicin is a humanized anti-CD33 antibody-calicheamicin conjugate that causes DNA double-strand breaks and apoptosis. Like with other monoclonal antibodies, the most common symptoms of reactions to gemtuzumab ozogamicin are fever and chills. Other symptoms include nausea, shortness of breath, and hypotension. These symptoms usually occur within 4 h after infusion. Pretreatment prophylactic regimens for reactions to this agent include acetaminophen and diphenhydramine given 15–30 min prior to infusion.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody against the CD52 molecule used in the treatment of leukemia and non-Hodgkin lymphoma. Side effects of this antibody range from mild to life-threatening and become less severe or disappear with gradual escalation of the dose. The most common symptoms of reactions to alemtuzumab included fever, rigor, nausea, vomiting, diarrhea, facial flushing, hives, wheezing, and hypotension. Prophylactic and treatment regimens for these reactions are similar to those for reactions to other monoclonal antibodies.

Systemic Reactions to Targeted Therapy

Sorafenib

Sorafenib is a small-molecule inhibitor of several tyrosine protein kinases (multikinase inhibitor) used for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma. Hypersensitivity reactions to sorafenib are rare (less than 1 % of patients), and the most common reactions are skin reactions and urticaria.

Erlotinib

Erlotinib is an oral tyrosine kinase (TK) inhibitor targeting the epidermal growth factor receptor that is used to treat locally advanced or metastatic non-small cell lung, pancreatic, and several other types of cancer. The most common symptoms of reactions to erlotinib that lead to drug discontinuation or dose reduction are rash, diarrhea, conjunctivitis, and vomiting. In particular, treatment with erlotinib may induce rash in up to 60–79 % of patients; this symptom is dose-related, but its presence may be related to improved prognosis. The rash most often resembles seborrheic dermatitis, but it may also manifest as palmar-plantar erythema with painful fissures and paronychia (Roe et al. 2006).

Bortezomib

Bortezomib was the first proteasome inhibitor approved for the treatment of multiple myeloma and mantle cell lymphoma. Immediate reactions to it are rare but can be serious and include angioedema and acute diffuse infiltrative pulmonary disease, which can be fatal.

Temsirolimus

Temsirolimus is a potent mammalian target of rapamycin inhibitor used to treat advanced renal cell cancer. The most common hypersensitivity reaction symptoms for this agent include edema, dizziness, and dyspnea. Hypersensitivity to temsirolimus occurs in about 5 % of patients who receive premedication (Bellmunt et al. 2008).

Imatinib Mesylate

Imatinib mesylate is a protein-TK inhibitor that is used in the treatment of Philadelphia chromosome-positive chronic myeloid leukemia. It suppresses proliferation and promotes apoptosis of bcr-abl–positive cell lines and fresh leukemic cells. The most common nonhematologic side effects of imatinib mesylate are edema, nausea/vomiting, diarrhea, myalgia, fatigue, rash, and headaches, although clinicians should be aware of the potential for cardiotoxicity of this agent. Patients who receive imatinib mesylate should be monitored for symptoms suggestive of decreased left ventricular function; if confirmed, use of angiotensin-converting enzyme inhibitors should be considered.

Management Strategies

When administering targeted drugs, educating patients about potential reactions to and side effects of these drugs is important, as they may not occur immediately. Management of cutaneous toxic effects of targeted drugs has yet to be standardized, although researchers have suggested using highly potent topical steroids combined with mupirocin, antihistamines (hydroxyzine), analgesics (nonsteroidal anti-inflammatory drugs), and antibiotics (doxycycline) given orally. Dermatologic symptoms of reactions to targeted agents are transient and improve with dose reduction or discontinuation, if needed. Management of other symptoms should consist of supportive treatment. If symptoms are severe and suggestive of hypersensitivity reactions, use of diphenhydramine, hydrocortisone, and epinephrine should be considered.

Systemic Reactions to Cytokines

Interferon

Recombinant interferons are widely used in the treatment of malignancies, viral infections, and autoimmune diseases. For malignancies in particular, these interferons can regulate gene expression and new enzyme synthesis, leading to altered cellular

proliferation and cell death. Acute reactions to interferons usually occur 2–8 h after infusion, but they rarely limit treatment. Common effects include nausea, vomiting, flu-like symptoms (low-grade fever, myalgia, and headaches), tachycardia, hypotension, and hypertension. Severe subacute effects appear 2–4 weeks after high-dose treatment and include anxiety, agitation, seizures, and coma, although they are reversible. Other rare effects include autoimmune and hemolytic anemia, thrombocytopenia, and myelosuppression. Usually, symptoms lessen with subsequent infusion of interferon, and treatment should be supportive according to the symptoms.

Interleukin-2

Side effects of interleukin-2 are dose-dependent. Owing to the potential for life-threatening effects, interleukin-2 should be given only subcutaneously or intravenously at low doses in the outpatient setting, with several hours of observation after infusion. Low-dose effects include anorexia, nausea, vomiting, fever, chills, myalgia, arthralgia, pruritus, and malaise. Interleukin-2 should be given intravenously at high doses in the inpatient setting, which may require intensive care monitoring. Severe symptoms of reactions to interleukin-2 include disorientation, psychosis, seizure, vascular leak syndrome, respiratory insufficiency, hypotension, shock, and coma. Fluid resuscitation, endotracheal intubation, and hemodynamic support may be needed. Interleukin-2 use should be discontinued at the first sign of neurotoxicity. A prophylactic regimen for interleukin-2 reactions should include acetaminophen (1 h prior to infusion and every 3 h for 2 doses), H_2 blockers (800 mg of cimetidine orally before infusion), and an antihistamine (50 mg of diphenhydramine orally 1 h before infusion and every 3 h for 3 doses). Treatment with meperidine and antiemetics may be needed for chills and nausea.

Cytotoxic Agents Affecting the Cardiovascular System

Vascular Endothelial Growth Factor/TK Inhibitor-Associated Hypertension

Bevacizumab is the most frequently used and studied vascular endothelial growth factor (VEGF) inhibitor. It is used in the treatment of many cancers, including colorectal, lung, breast, and ovarian cancer; glioblastoma; and renal cell carcinoma. One of the main side effects of all VEGF inhibitors is hypertension. Specifically, authors have reported hypertension in up to 32 % of patients receiving bevacizumab, with grade 3 hypertension present in 11–16 % of patients, particularly those receiving high doses. Concomitant use of 5-fluorouracil may increase the incidence of hypertension (Izzedine et al. 2009). However, hypertension may be related to delayed time to progression of renal cell carcinoma in patients who receive bevacizumab. The rate of hypertension varies according to TK inhibitor, with low rates

seen with nilotinib and dasatinib (1–10 %), higher rates seen with sorafenib and sunitinib (9–30 %), and the highest rates seen with vandetanib, axitinib, and pazopanib (33–40 %). Researchers have noted grade 3 hypertension in 3–18 % of patients receiving these TK inhibitors. In contrast, use of crizotinib, gefitinib, erlotinib, imatinib, lapatinib, and ruxolitinib is not associated with new or worsening hypertension.

Elevated blood pressure can be quite refractory to treatment with many antihypertensive agents and results from inhibition of the vasodilatory effect of VEGF on small arterioles and venules but not medium-sized arteries or veins. VEGF is believed to cause vasodilatation via activation of protein kinase B, which stimulates phosphorylation of endothelial type nitric oxide synthase, resulting in enhanced nitric oxide production, which leads to dilation of small vessels. Inhibition of endothelial type nitric oxide synthase also leads to decreased production of prostacyclins and increased expression of plasminogen activator inhibitor-1 in tissues, which may worsen hypertension. A similar mechanism is suggested for TK inhibitors, although researchers have demonstrated microvascular rarefaction (decreased numbers of small arteries and arterioles) with the use of some agents, such as telatinib (Izzedine et al. 2009).

Management Strategies

Angiotensin-converting enzyme inhibitors prevent expression of plasminogen activator inhibitor-1 and can be helpful in controlling VEGF/TK inhibitor-induced hypertension. Calcium channel blockers (CCBs), particularly nifedipine, are very effective in controlling elevated blood pressure associated with the use of VEGF inhibitors, and a recent study demonstrated benefits of using CCBs as prophylaxis for the development or exacerbation of such hypertension. However, nifedipine can increase VEGF secretion, and nondihydropyridine CCBs such as diltiazem and verapamil are cytochrome P450 3A4 inhibitors; their use should be avoided in patients receiving TK inhibitors. Until further studies are available, we recommend the use of dihydropyridine CCBs only (with the exception of nifedipine). Nebivolol is a β_1-adrenergic blocker with dilating activity in small vessels, leading to decreased peripheral resistance, and its activity is mediated by the endothelial L-arginine nitric oxide pathway.

Treatment of hypertension should be personalized for each patient, taking into account other comorbidities and cardiac risk factors. Patients should be carefully evaluated for signs of hypertension prior to starting treatment with VEGF inhibitors. If a patient is hypertensive (or prehypertensive with a cardiac risk factor), prophylaxis with dihydropyridine CCBs other than nifedipine should be considered. After initiation of treatment, we recommend angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers as the first line of therapy, particularly in patients with proteinuria and creatinine levels less than 2 mg/dL but not hyperkalemia or renal artery stenosis. The second line of treatment should include dihydropyridine

CCBs other than nifedipine (e.g., amlodipine, felodipine). The third line of treatment includes nebivolol; if the patient has a history of coronary artery disease, a trial of a short-acting nitrate should be considered and, if used and proven to be effective, converted to long-acting agents. If all three lines of treatment fail, consider treatment with diuretics and α-blockers. Clonidine should be considered on the day of infusion if an acute drop in blood pressure is required.

Anthracyclines and Cardiomyopathy

Anthracyclines are commonly used in the treatment of many cancers, including acute myeloid leukemia (daunorubicin, doxorubicin, idarubicin, and mitoxantrone), bladder cancer (doxorubicin and valrubicin), breast cancer (doxorubicin and epirubicin), gastric carcinoma (doxorubicin), Hodgkin lymphoma (doxorubicin), sarcomas (doxorubicin and liposomal daunorubicin), lung cancer (doxorubicin), multiple myeloma (liposomal doxorubicin), ovarian cancer (liposomal doxorubicin), prostate cancer (mitoxantrone), and thyroid cancer. They inhibit both DNA and RNA synthesis and topoisomerase II activity, blocking DNA transcription and relocation.

Risk factors for cardiomyopathy include the total dose of anthracycline given, age, prior heart disease, and cardiovascular disease-related factors (e.g., diabetes, hypertension). Acute toxic effects of anthracyclines are usually transient and can be managed medically. This may be followed by an asymptomatic phase that progresses to symptomatic diastolic dysfunction and then to symptomatic systolic dysfunction. The risk of anthracycline-related cardiomyopathy is highest in the first year, but when it occurs, it is not clinically different from cardiomyopathy of other etiologies.

Management

We recommend baseline cardiac evaluation with an echocardiogram or gated study prior to starting treatment with any anthracycline. Patients should be monitored for clinical clues suggestive of early cardiomyopathy (e.g., resting tachycardia, jugular vein distension, physical signs suggestive of cardiomyopathy, new murmurs or gallop sounds, weight gain, edema, crackles). Some investigators have suggested measurement of brain natriuretic peptide level before and after chemotherapy and troponin level 5–7 days after each cycle of chemotherapy or more frequently. Many researchers have also suggested follow-up echocardiograms on different schedules, even in asymptomatic patients, ranging from yearly in childhood survivors to 6, 12, and 24 months and then every 5 years after treatment. Several studies have addressed prevention of cardiomyopathy in high-risk patients with the use of modified slow regimens, dexrazoxane, and liposomal formulations with varying degrees of cardioprotection. Once anthracycline-related cardiomyopathy occurs, it is clinically similar to cardiomyopathy of other etiologies, and traditional management of cardiomyopathy can be performed.

Drug Extravasation

Extravasations occur with 0.1–6.5 % of chemotherapy infusions and can significantly damage tissues surrounding the target site (Clamon 1996). Factors that can increase the risk of extravasation include fragile, small, or sclerosed veins; lymphedema; superior vena cava syndrome; altered mental status; and use of pumps or prolonged infusions via peripheral veins.

Clinical Manifestations

The clinical manifestations of extravasation injury depend on the type of chemotherapeutic agent being infused. Chemotherapeutic agents can be classified according to their potential for causing local injury as nonvesicants, vascular irritants, and vesicants (Table 11.2). Extravasation of nonvesicants does not damage surrounding tissues. Extravasation of a vascular irritant may cause pain, aching, tightness, and phlebitis of the involved vein, and tissue injury is immediate. However, the extravasated drug is quickly metabolized and degraded, and gross necrosis does not occur. Vesicants, on the other hand, remain in tissue, frequently binding to DNA, and cause necrosis. Because vesicants cannot be metabolized locally, as one cell dies, the vesicant inside it is released and taken up by another cell, leading to necrosis. The onset of symptoms of vesicant extravasation may be immediate or delayed for days to weeks, and the symptoms may be mild initially. Early symptoms may include local burning, tingling, mild erythema, swelling, and pruritus. Vesicants can produce necrosis and ulcerations even when conservative local management is used. They can also cause recall dermatitis in patients with prior extravasation or irradiation of the same site. These are low-grade skin reactions with ulcerations and are more common with extravasation of anthracyclines and paclitaxel than of other agents (Du Bois et al. 1996). Mild to moderate symptoms of extravasation include pain at the site, moderate swelling, blanching of the area, skin that is cool to the touch, and brisk capillary refill. With severe extravasation, the capillary refill is prolonged (more than 4 s), and swelling can be severe.

Management Strategies

The best approach to management of drug extravasation is prevention. For example, if multiple infusions of vesicants are planned, placement of central venous access systems should be strongly considered. In addition, creation of institutional policies for infusion of potential vesicants and management of extravasation should be considered. All health care personnel handling chemotherapeutic agents should be trained in the use of prevention techniques and how to monitor for early signs of potential extravasation (e.g., no blood return on aspiration, spontaneous change in

Table 11.2 Vesicants and vascular irritants

Vesicants
Cisplatin (Platinol)
Dactinomycin (actinomycin D; Cosmegen)
Daunorubicin (daunomycin; Cerubidine)
Doxorubicin (Adriamycin)
Epirubicin (Ellence)
Idarubicin (Idamycin)
Mechlorethamine (nitrogen mustard; Mustargen)
Mitomycin C (Mutamycin)
Mitoxantrone (Novantrone)
Oxaliplatin (Eloxatin)
Vinblastine (Velban)
Vincristine (Oncovin)
Vinorelbine (Navelbine)
Vascular irritants
Abraxane
Arsenic trioxide (Trisenox)
Bleomycin (Blenoxane)
Bortezomib (Velcade)
Busulfan (Busulfex)
Carboplatin (Paraplatin)
Carmustine (BiCNU)
Cisplatin (Platinol)
Cladribine (Leustatin)
Dacarbazine (DTIC-Dome)
Docetaxel (Taxotere)
Etoposide (VePesid)
Etoposide phosphate (Etopophos)
Fluorouracil
Gemcitabine (Gemzar)
Ifosfamide (Ifex)
Irinotecan (Camptosar)
Liposomal cytarabine (DepoCyt)
Liposomal daunorubicin (DaunoXome)
Liposomal doxorubicin (Doxil)
Liposomal vincristine (Marqibo)
Melphalan (Alkeran)
Paclitaxel (Taxol)
Plicamycin (Mithracin)
Teniposide (Vumon)
Thiotepa
Topotecan (Hycamtin)

Adapted from The University of Texas MD Anderson Cancer Center. *Current Institutional List of Vesicant Agents and Vascular Irritants*. May 2009 revision. Houston, TX: The University of Texas MD Anderson Cancer Center; 2009

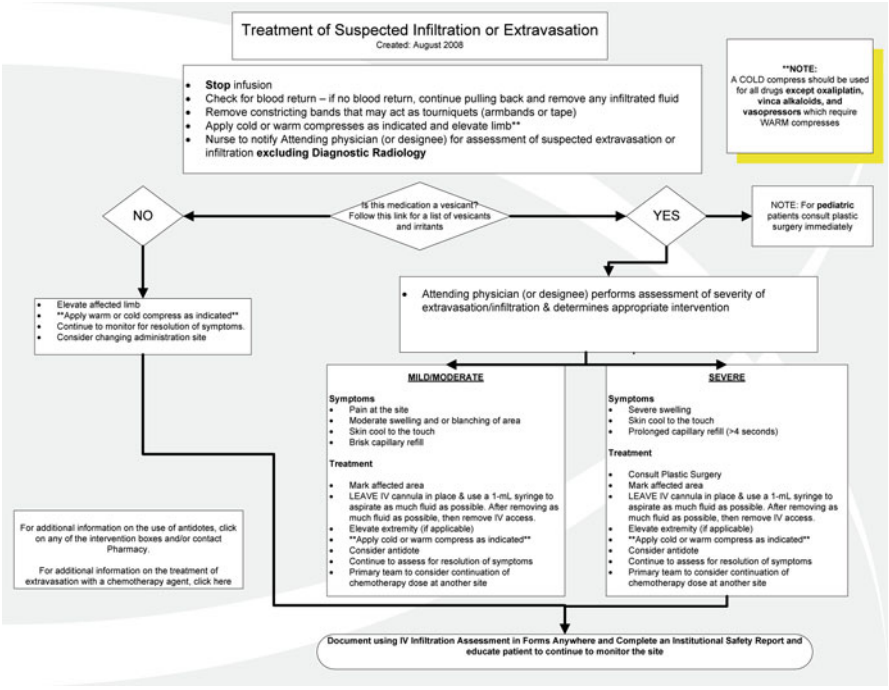

Fig. 11.2 Schema of conservative management of extravasation injuries at MD Anderson. *IV* intravenous

the infusion rate). We also recommend that patients receive educational materials regarding the specific drug to be infused prior to treatment with a vesicant.

Treatment of extravasation injuries is somewhat controversial, varying from conservative local care to early surgical debridement to the use of select antidotes. This controversy is the result of limited clinical studies and discordance between animal and human data. Conservative management of extravasation injuries in our institution includes the following steps (Fig. 11.2):

- Stop the intravenous infusion.
- Do not remove the catheter.
- Do not infuse other fluids or medications through the site.
- Remove any infiltrated fluid.
- Apply cold compresses and elevate the affected limb. Apply warm compresses to sites of extravasation of oxaliplatin, vinca alkaloids, and vasopressors.
- Alert a responsible health care provider.
- If the medication is a vesicant, perform further assessment and determine appropriate treatment.

Physicians performing the assessment should first determine the severity of the extravasation, mark the affected area, and consider the use of an antidote if one is

Table 11.3 Guidelines for use of extravasation antidotes

Antidote	Drug	Guideline
50 % dimethyl sulfoxide cream	Anthracycline extravasation	Apply topical cream and allow it to dry; repeat 4 times daily for 2 weeks.
Hyaluronidase (Amphadase)	Paclitaxel, vinka alkaloids, all extravasations	Infuse a total of 1 mL (150 U) in 5–10 subcutaneous injections of 0.1–0.2 mL per injection into the affected area to up to 250 U or until symptoms resolve.
Dexrazoxane	Anthracycline extravasation	(1) Infuse 1000 mg/m^2 on days 1 and 2 (maximum dose, 2 g) followed by 500 mg/m^2 on day 3 (maximum dose, 1000 mg) intravenously over 2 h. (2) The infusion should begin no longer than 6 h after extravasation and should be given in a large vein in an area remote to the extravasation. (3) If cooling techniques are used, withhold cooling 15 min before and after the infusion.
10 % sodium thiosulfate (Tinver)	Cytotoxic drug extravasation	Prepare a 0.17-mol/L solution (mix 4 mL of 10 % Tinver with 6 mL of sterile water). Inject 2 mL subcutaneously into the extravasation site.

available (Table 11.3). A plastic surgery consultation is recommended for a severe extravasation injury, as the associated likelihood of development of ulcers is increased. Prior to discharge, patients must be educated about the need to carefully monitor the extravasation site for associated symptoms and signs for at least 48 h. A follow-up visit to a physician within 3–4 days is also recommended.

Key Practice Points

- Educate patients regarding how to monitor their symptoms for side effects or hypersensitivity reactions and call for assistance.
- Develop monitoring protocols for chemotherapy and educate infusion unit staff.
- Maintain lists of vesicants and vascular irritants as well as extravasation protocols readily available in the infusion unit.
- Consider placement of central venous access systems if multiple infusions of vesicants are planned.
- Evaluate patients' blood pressure, cardiac function, and risk potential prior to starting treatment with potentially cardiotoxic agents.
- Consider premedications and desensitization regimens.
- If an immediate reaction or extravasation is suspected, stop the infusion, activate the appropriate protocol, and call the supervising physician.
- Monitor hemodynamics and symptoms.
- If severe symptoms or hypersensitivity reactions occur, consider using diphenhydramine, hydrocortisone, H_2 blockers, and epinephrine as needed.
- Provide aggressive supportive treatment of other symptoms.

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Chapter 12
Palliative Care in the Emergency Center

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Contents

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Chapter Overview

Palliative care is a relatively new discipline in medicine that focuses on the assessment and management of suffering in patients with advanced illnesses such as cancer. The field of oncologic emergency medicine is also an emerging discipline that focuses on emergency medical care for a unique patient population that differs substantially from the general emergency medicine population. In this chapter, we review the general principles of palliative care as it applies to the emergency care of cancer patients, specifically, those with advanced cancer. This chapter is not intended to be a comprehensive review. Rather, the goal is to provide the reader with a practical, general overview of common palliative care issues. Topics covered in this chapter include pain management, fatigue and weakness, anorexia and cachexia, ethics, communication, and interdisciplinary palliative care teams.

Introduction

Palliative care is defined by the World Health Organization as improvement of the quality of life of patients and their families facing the problems associated with life-threatening illness via prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems—physical, psychosocial, and spiritual. The main focus of palliative care is relief of symptoms rather than treatment of the underlying disease process. However, palliative care can be provided simultaneously with disease-modifying treatment.

In comparison, emergency medicine is a discipline traditionally viewed as curative, in which care is focused on quick assessment, identification, resuscitation, and initiation of appropriate treatment. Therefore, integration of palliative care into the emergency care of cancer patients may sound counterintuitive. However, many cancer patients who present to emergency centers suffer from advanced illnesses and have a great deal of physical and psychosocial distress. In fact, in the setting of emergency care of cancer patients, palliative care principles and practices are frequently used, ranging from pain and symptom management for patients who present with treatment-related toxicity to management of impending death and the distress associated with it. In addition, emergency physicians are frequently faced with challenging end-of-life situations in which decisions regarding the goals of therapy are made quickly to avoid inappropriate invasive interventions for patients whose wishes are directed toward comfort and quality of life. Therefore, emergency medicine physicians must be competent in the basic principles and practices of palliative medicine. In this chapter, we review the most commonly encountered and applicable palliative care issues in the emergency care of cancer patients.

Pain Management

Pain is the most common reason for emergency center visits. Cancer patients frequently present to the emergency room because of uncontrolled cancer-related pain, but they can also present with non-cancer-related pain issues. In these patients, pain can be classified as acute, chronic, or acute on chronic.

Although the exact etiology of cancer pain is unknown, pain usually signifies an underlying inflammatory process in the cancer microenvironment. Cancer and immune cells produce and secrete inflammatory mediators and cytokines that activate the primary afferent neurons, which in turn stimulate nociceptive secondary neurons in the spinal cord, leading to enhanced responsiveness to noxious stimuli. In the majority of cancer patients, pain results from the presence of a tumor mass. However, treatment may cause significant pain, such as mucositis or esophagitis resulting from chemotherapy or radiation therapy.

Several guidelines for the management of cancer pain are available from the World Health Organization, National Comprehensive Cancer Network, and Agency for Healthcare Research and Quality. In this section, we focus on the pertinent pain management issues for cancer patients in the emergency room. Chronic and maintenance pain management are beyond the scope of this chapter.

Assessment of Pain

Medical History

When assessing cancer pain in the emergency setting, the general factors of intensity, location, onset, duration, radiation, and exacerbating and alleviating factors should be assessed. In addition, the potential pathophysiology of pain—whether it is somatic, visceral, or neuropathic—and temporal factors—whether the pain is continuous, intermittent, breakthrough, or incidental—should be evaluated. The patient's tumor history and previous treatment should be evaluated to determine the potential etiology of the pain. A careful medical history, including both continuous and breakthrough medication use and compliance, is crucial.

Functional Evaluation

The patient's ability to perform daily activities, including exercise, ambulation, and household chores, should be evaluated. Also, range-of-motion and functional limitations owing to pain should be assessed. In addition, re-evaluation of patient function after analgesia should be considered. Patients in the emergency department are commonly limited to their beds; therefore, their pain control may be falsely interpreted as adequate. Patients should be encouraged to increase their function in the emergency department to levels closer to those at home so that true pain control can be achieved.

Psychosocial Issues

Psychosocial distress is common in cancer patients and their caregivers. Severe psychologic distress such as anxiety and depression can manifest as physical distress, for example, acute pain and nausea. When psychosocial distress is detected or suspected, involvement of appropriate health care providers such as social workers, counselors, and psychiatrists can aid in the treatment of pain. In addition, evaluation of the patient's history of substance abuse using simple assessment tools such as the alcoholism screening CAGE questionnaire (Have you ever felt the need to Cut down your drinking, felt Annoyed by criticism of your drinking, had Guilty feelings about drinking, and taken a morning Eye opener?) is important. Similarly, the presence of delirium or other cognitive impairments may complicate assessment of pain, especially with nocturnal exacerbation. This is particularly important for patients who have been taking chronic opioids, are dehydrated, and/or have renal dysfunction.

Chronic Pain

Chronic pain in cancer patients can be a significant challenge owing to their frequent use of opioid analgesics and the resultant tolerance, dependence, and opioid-induced toxicity and, in some circumstances, concerns about opioid addiction and diversion. In addition, cancer patients can experience exacerbation of their underlying pain or new pain issues when presenting to the emergency center with acute or chronic pain requiring upward titration of their opioid dosages. Acute or chronic pain can occur as a result of cancer or treatment-related complications such as infection, hemorrhage, thrombosis, bone fracture, an obstructed viscus, nerve compression, and mucositis.

Cancer patients with chronic pain can be either opioid-naïve or opioid-tolerant. In this chapter, patients receiving weak opioids such as hydrocodone are considered to be opioid-naïve. Caution should be taken when prescribing and titrating opioid analgesics for opioid-naïve patients, as they have increased chances of experiencing acute respiratory depression and neurotoxicity with rapid titration. In comparison, opioid-tolerant patients tend to have lower chances of suffering from respiratory depression when prescribed appropriate doses.

Choosing a specific opioid is often less important than correct dosing of it, as side effects are similar for the commonly prescribed drugs. When managing chronic pain, anticipation, counseling, and prevention of common side effects such as constipation can improve compliance. In addition, counseling and family education regarding the common misunderstandings about opioids are paramount. The oral route is the preferred one for administration of opioids. However, alternate routes of administration, such as the parenteral route, are important in the management of acute crises. Use of adjuvant analgesics is necessary for good pain control, but they

have important differences in indications, usage, and side effects from those of opioids. Pain management is a basic professional and humanitarian responsibility of the skilled emergency medicine physician.

Acute Pain

Acute pain in cancer patients can present as either a new pain syndrome or exacerbation of chronic pain. In both cases, prompt attention to the etiology and management of acute pain is crucial to preventing intractable pain. Patients who present with new-onset pain are likely to be opioid-naïve. Therefore, careful initiation and titration of opioids for these patients is warranted to avoid excess sedation and opioid-induced respiratory depression. In comparison, patients who present with acute exacerbation of chronic pain are likely to be opioid-tolerant, and opioids are frequently underdosed for them if proper dosage calculation is not done.

Pain management in opioid-naïve patients should follow the proposed World Health Organization ladder, starting with nonopioid analgesics and titrating up to weak opioids when needed. Strong opioid analgesics should be reserved for patients with severe intractable pain who do not have responses to the first steps in the pain ladder. However, emergency physicians are frequently faced with severe pain in opioid-naïve patients. In such circumstances, parenteral administration of strong opioids is required, and physicians should be familiar with the equivalent potencies of these opioids and frequently assess the responses to and potential side effects of these drugs.

When managing acute pain in cancer patients with chronic pain who are opioid-tolerant, the total morphine-equivalent daily dose (MEDD) should be calculated. This can help direct the appropriate dosing of rescue medications for control of acute pain exacerbation. In general, the rescue opioid dose should be 10–15 % of the total daily opioid dose.

Researchers have proposed several strategies for managing acute pain in cancer patients. However, clear evidence supporting the use of one strategy over another is lacking. Acute pain management in cancer patients requires rapid dose titration until the onset of analgesia followed by maintenance therapy with opioids based on the loading dose and pre-titrated opioid dose. This is followed by evaluation of the underlying cause of acute or suddenly worsening pain, if appropriate. Based on our experience at The University of Texas MD Anderson Cancer Center, we suggest the following 8-step approach when managing acute pain in cancer patients previously receiving opioids.

1. Proper assessment of the pain syndrome, including its location, severity, onset, and exacerbating and alleviating factors.
2. Assessment of physical and psychosocial factors that can influence the pain experience.
3. Calculation of the MEDD (Table 12.1).

4. Prescription of 10–15 % of the MEDD as the rescue dose.
5. Assessment of response to an opioid medication within 15 min of delivery of the initial dose. The initial dose can be repeated if adequate analgesia is not achieved.
6. Assessment of function in addition to the subjective pain reported by the patient.
7. Adjustment of the basal opioid dose either by adding the rescue doses needed over the past 24 h or an incremental increase by 30 %.
8. For patients whose pain is refractory to these initial steps, prompt consultation with pain management or palliative care experts, if available, is recommended.

Opioid Analgesics

In general, opioids are classified as weak or strong. Weak opioids include hydrocodone, codeine, and tramadol. Strong opioids include morphine, hydromorphone, oxycodone, oxymorphone, meperidine, fentanyl, sufentanil, methadone, and levorphanol (Table 12.1). Morphine, hydromorphone, and fentanyl are frequently used parenterally to control pain in the emergency setting.

Opioid partial agonists and mixed agonist-antagonists have limited roles in cancer pain management owing to their ceiling effect and mixed receptor activity. In addition, they exhibit increased central nervous system activity and pose a withdrawal risk in patients already taking opioid agonists.

Table 12.1 Strong opioid conversion

Opioid (route)	Conversion from oral opioid to oral morphine	Conversion from parenteral opioid to same oral opioid	Initial rescue dose in an opioid-naïve adult
Morphine (PO, IV)	1	1.0:2.5	PO 5–10 mg, IV 2–4 mg
Hydromorphone	5	1:2	PO 1–2 mg, IV 0.5–1.0 mg
Fentanyl (patch, lozenges, IV)	Consult chart supplied by manufacturer	Consult chart supplied by manufacturer	IV 25 μg
Oxymorphone (PO, IV)	3	10	PO 5 mg, IV 0.5 mg
Meperidine[a] (PO, IV)	0.1	4	IV 25 mg
Oxycodone (PO)	1.5	NA	PO 5 mg
Methadone (PO, IV)	Variable (based on MEDD)	1:2	NA

PO by mouth, *IV* intravenous, *NA* not available

[a]Meperidine not recommended for chronic opioid use

(1) Take the total amount of opioid that effectively controls pain in 24 h. (2) Multiply by the conversion factor in the table and give 30 % less of the new opioid to prevent partial cross-tolerance. (3) Divide by the number of doses per day

Adjuvant Analgesics

Analgesics can be beneficial when added to opioids in certain pain situations. For example, antidepressants such as amitriptyline and anticonvulsants such as gabapentin can be useful in management of neuropathic pain syndromes such as chemotherapy- and diabetes-induced neuropathy. Bisphosphonates are frequently used for management of painful bone metastases. Also, corticosteroids such as dexamethasone can be added when managing neuropathic, visceral, or bone pain and are particularly useful in controlling the pain associated with spinal cord compression.

Fatigue and Weakness

Fatigue is one of the most common symptoms in patients with advanced cancer. The incidence rate of cancer-related fatigue (CRF) ranges from 60 % to 90 %. CRF is defined as an unusual, persistent, subjective sense of tiredness related to cancer or its treatment that interferes with usual functioning. Fatigue can greatly decrease a patient's quality of life and interfere with a patient's ability to perform physical and social activities. It may also affect a patient's decision making regarding future treatments, leading to refusal of potentially curative or supportive treatment. Fatigue has a major negative impact on both the patient and his or her family. It interferes with activities of daily life and robs patients of time and energy required to engage in routine activities with their loved ones. This greatly decreases the patient's quality of life.

In the majority of patients with advanced cancer, the etiology of fatigue is unclear, but its effects are consistent. Previous studies revealed that CRF has a multidimensional etiology in these patients. Different mechanisms directly or indirectly impact brain function to cause the subjective symptom of fatigue. In recent years, researchers have found that several cytokines and other pro-inflammatory mediators produced by the host in response to the presence of cancer are associated with fatigue. Some patients present with transient fatigue caused by reversible factors such as infection, anemia, dehydration, and metabolic and electrolyte disturbances.

Fatigue is a common reason for emergency room visits in patients with advanced cancer. In a study conducted at the MD Anderson Emergency Center, severe fatigue (rated as 7 or higher on a scale of 0–10) was reported by more than half of the patients upon admission. Patients with severe fatigue were likely to be unstable or unable to be discharged from the hospital.

Assessment of Fatigue

Several tools are available for the assessment of CRF. The severity of fatigue can be quickly assessed using a numerical scale from 0 to 10, in which 0 represents no fatigue and 10 represents the worst fatigue imaginable. Comprehensive assessment

tools such as the Functional Assessment of Chronic Illness Therapy-Fatigue subscale are more multidimensional and consider the impact of fatigue on activities and function. In addition, assessment of potentially reversible causes of fatigue, such as anemia, infection, dehydration, mood disorder, drugs, and metabolic and electrolyte disturbances, can further aid the management of fatigue in these patients.

Management of Fatigue

Despite its prevalence, severity, and effects on quality of life in patients with advanced cancer, the available treatment options for CRF are limited. In the emergency setting, management of fatigue should focus on treating its underlying reversible causes first. Pharmacologic treatment of fatigue can be attempted for a patient with chronic CRF in whom treatment of its potentially reversible causes does not result in subjective improvement or if no reversible causes of the fatigue are identified. Consultation with symptom management and palliative care experts is highly recommended for such patients to improve the long-term effectiveness of treatment. Pharmacologic agents that can be used for treatment of fatigue include corticosteroids, psycho-stimulants such as methylphenidate, and antidepressants. Furthermore, testosterone replacement can be considered to treat fatigue in male patients.

Anorexia and Cachexia

Anorexia and cachexia are among the most debilitating and distressing complications of cancer and its treatment. Anorexia is loss of appetite or desire to eat, whereas cachexia is a syndrome characterized by involuntary weight loss, fat and muscle wasting, immune dysfunction, and various metabolic and hormonal alterations. In cancer patients, cachexia is frequently associated with negative health outcomes, including increased risk of infection, poor tolerance of cancer treatments, and decreased survival durations. Anorexia can be particularly distressing to families and caregivers because of fear of starvation and wasting. Attempts to force-feed a patient can result in food aversion and exacerbate the problem.

The etiology of anorexia-cachexia syndrome is complex and multidimensional. Increased levels of inflammatory cytokines are implicated to play a role in the pathogenesis of anorexia and cachexia. Hormonal changes such as low testosterone level, insulin resistance, growth hormone deficiency, and ghrelin resistance also can play a role. Decreased food intake owing to nausea, dysgeusia, and early satiety can contribute to cachexia. Psychosocial factors such as depression, anxiety, and lack of support can play a role in the etiology of anorexia and cachexia in cancer patients.

Assessment

Assessment of anorexia and cachexia includes a history focused on the patient's nutritional intake and related symptoms as well as a directed physical examination to screen for signs of cachexia, such as temporal wasting and muscle loss.

As with other cancer-related complications, a careful review of pertinent systems and concurrent symptoms is essential to the multidimensional assessment of anorexia and cachexia. Laboratory screening for metabolic and hormonal causes of cachexia can help direct management in the outpatient setting but may not be applicable in the emergency room, as many of the relevant laboratory test results are not immediately available to physicians performing direct management. Assessment of hydration status is also important, as many patients with anorexia have decreased fluid intake, as well.

Management

Anorexia and decreased fluid intake are common reasons for emergency center visits. Patients who are unable to maintain adequate food and fluid intake and have resultant weakness and failure to thrive may need hospital admission for management of their nutritional and fluid needs.

A standard specific agent for management of anorexia and cachexia in cancer patients has yet to be identified. Researchers have shown that most cancer patients have secondary symptoms that can lead to anorexia and cachexia, such as nausea, constipation, and dysgeusia. Therefore, identification and treatment of potential precipitating factors is crucial to the management of anorexia and cachexia in these patients. Appetite-stimulating agents have exhibited promise in treating anorexia in some patients. These include progestational agents such as megestrol acetate, corticosteroids such as dexamethasone, and cannabinoids such as dronabinol.

Nonpharmacologic management of anorexia and cachexia should integrate nutritional support and counseling, exercise, and physical therapy when appropriate and psychosocial support and counseling for patients and their caregivers.

Ethics

Emergency medicine clinicians are frequently faced with difficult patient and family situations that require application of basic ethical principles to direct appropriate medical care. Ethical decision making for patients with advanced cancer can be complex and is influenced by several patient, family, and clinician factors. These include but are not limited to the patient's autonomy, the patient's and family's treatment goals, communication, disclosure and confidentiality, informed decision

making, psychosocial and spiritual factors, and interrelationships among the patient, family, and clinicians.

Ethical considerations for cancer patients are complex. Herein we focus on the concept of ethical principles, which implies that guiding laws or practices determine the rightness of certain actions. These principles include the following:

- Nonmaleficence: the physician should cause no harm to the patient
- Beneficence: the physician should help the patient
- Autonomy: a competent patient has the right to accept or reject medical treatment
- Justice: the physician should act with fairness toward the patient
- Benefit versus risk: the benefit of medical treatment should be greater than its risk
- Sanctity of life: human life is considered worthy of respect and preservation

These ethical principles can be influenced by several factors, including cultural and religious issues and familial relationships. For example, in most Eastern cultures, family-centered care and decision making are valued over autonomy, whereas in Western cultures, the patient's autonomy is valued over family-centered decision making. In addition, in some countries, decision making is made by physicians in a paternalistic fashion without consulting with the patient or family. In contrast, in developed countries, patients are provided with the treatments of their choice even when their physicians disagree with the choices.

These ethical principles commonly conflict with each other. For example, patients with cancer may request chemotherapy during advanced stages of the disease; the principle of autonomy gives them the right to do so. However, if the clinician firmly believes that chemotherapy can cause more harm than benefit, he or she is supported by the ethical principles of nonmaleficence and benefit versus risk in withholding chemotherapy from these patients, as the obligation to do no harm supersedes all other ethical principles. Another example of balancing ethical principles is the prescription of opioids and sedatives to patients with advanced cancer with the intention of relieving their suffering while recognizing that the interventions may shorten their lives. In these situations, the doctrine of double effect justifies the use of potentially life-shortening treatments with the sole intention of providing benefits and relief.

Advance Directives

An advance directive is a legal document that communicates patients' treatment preferences and chosen agents or power of attorney when they are unable to make decisions for themselves. Advance directive documents differ according to state and country. In most states, advance directive documents include a living will or directive to physicians, a medical power of attorney, and a do-not-resuscitate order. In general, advanced directives can be changed or revoked by the patient at any time and for any reason. Therefore, these preferences should be confirmed by the patient before executing them.

Communication

In the emergency setting, communication and delivery of bad news can pose significant challenges to emergency medicine physicians. Several factors can affect or interfere with effective communication in this setting. These factors include the curative focus of treatments provided in the emergency department, lack of training on how to communicate with patients with advanced cancer, a lack of time and space, a lack of an ongoing physician-patient relationship, rapid deterioration of the patient's condition, and patient- and family-related factors. Also, giving bad news is a complex task that requires preparing for the discussion, gathering and delivering information, and addressing emotions. In addition, studies have demonstrated that cancer patients prefer to discuss end-of-life issues with their primary oncologists or treating physicians. Taken together, all of these factors can make delivering bad news in the emergency setting difficult and distressing for both the patient and clinician.

Of several proposed strategies for delivering bad news to cancer patients, the SPIKES protocol is probably the most widely used. This protocol, which breaks the discussion into six basic steps, can be applied when delivering bad news and discussing end-of-life transitions and do-not-resuscitate status.

Step 1: SETTING UP and preparing for the interview.
Step 2: Finding out the patient's PERCEPTION of the illness.
Step 3: Getting an INVITATION to deliver information.
Step 4: Giving the patient KNOWLEDGE about his or her illness.
Step 5: Responding to the patient's EMOTIONS.
Step 6: Communicating a clear treatment STRATEGY and SUMMARY of the encounter.

Interdisciplinary Team Approach

An interdisciplinary team is a group of people from different disciplines who assess and plan care in a collaborative manner. A common goal is established, and members of each discipline work to achieve it. In the emergency setting, each team member plays a pivotal role in improving the patient's quality of life. An interdisciplinary team approach is required to deliver effective palliative care. Core members of the team include physicians, social workers, nurses, case managers, and chaplains. Extended team members can include pharmacists; allied health professionals such as physical, occupational, and speech therapists; nutritionists; and nursing assistants. Although a detailed discussion of the individual roles of these team members is beyond the scope of this chapter, emergency medicine physicians must familiarize themselves with the services provided by these team members.

Clear communication among team members, strong leadership, and clear definition of goals that allow for flexibility when appropriate are paramount to an

interdisciplinary team's success. In contrast, lack of commitment and trust among team members and poor communication are common pitfalls that can lead to disruption of the team's structure and function.

Key Practice Points

- Pain is a multidimensional symptom that is influenced by physical, psychologic, and emotional factors.
- When managing acute pain in opioid-tolerant patients, the total MEDD should be calculated, and the rescue dose should be 10–15 % of the total daily dose.
- Opioid medications represent the mainstay of pain management in cancer patients.
- Partial opioid agonists and mixed agonist-antagonists have a limited role in the management of cancer pain.
- Adjuvant analgesics can be beneficial in the management of neuropathic pain and painful bony metastases.
- Fatigue can impair both physical and mental function in cancer patients.
- Attempts should be made at identifying and treating any potentially reversible causes of fatigue, such as anemia, infection, dehydration, and metabolic disturbances.
- Anorexia can be particularly distressing to patients and families owing to fear of starvation. Counseling should be provided to families to avoid force-feeding, which can lead to food aversion.
- Patients unable to maintain adequate food and fluid intake may need hospitalization to address their nutritional and fluid needs.
- The ethical principle of nonmaleficence or do no harm can aid the clinician in decision making regarding difficult end-of-life situations.
- Advance directives are legal documents intended to communicate patients' wishes when they are unable to make decisions for themselves. Advance directives should be acknowledged and respected when giving treatment to patients at the end of life.
- Communicating bad news is anxiety-provoking for both the patient and clinician. The SPIKES protocol can assist the clinician with proper delivery of bad news.
- An interdisciplinary team approach is essential for palliative care delivery in the emergency setting.

Suggested Readings

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Chapter 13
Psychiatric Emergencies

Seema M. Thekdi and Sara Wood

Contents

Chapter Overview

The goal of this chapter is to provide an overview of the psychiatric emergencies that develop in cancer patients. In the section on agitation, a differential diagnosis is provided and discussed, as are workup and intervention strategies. Causes of agitation in the oncology setting are reviewed, specifically, delirium, adverse medication effects, substance intoxication and withdrawal, and exacerbation of psychiatric disorders. Specific medical and psychiatric conditions that may manifest as

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agitation in the cancer patient are detailed. Approaches to both nonpharmacologic and pharmacologic management of the agitated cancer patient are included. The ensuing section on suicide provides an understanding of the prevalence of suicide in cancer patients, risk factors associated with increased rates of suicide, and critical time points in the course of cancer treatment when clinical monitoring of suicidality and depression should be heightened. Tips on screening and evaluation as well as initial management steps are presented.

Introduction

Medical professionals working in the oncology setting are often on the front line when psychiatric emergencies develop in their patients. A number of clinical situations require urgent psychiatric assessment and intervention. Agitation is a potentially dangerous symptom commonly arising in the context of acute delirium. Additionally, medication side effects, substance intoxication or withdrawal, and exacerbation of underlying psychiatric disorders may come to clinical attention when a patient becomes agitated. Depression, anxiety, mania, and psychosis may develop or worsen during cancer treatment. Understanding the causes of agitation in cancer patients is key for oncology professionals, and they must be prepared with management strategies to keep patients and staff members safe during emergency situations.

Suicidal thinking may develop in a cancer patient owing to emotional or physical suffering. Although challenging, medical professionals must screen for suicidality and determine when a patient may be in danger of harming himself or herself. Understanding factors that increase the risk of suicide is helpful for the clinician in identifying patients for more intensive and frequent screening. Oncology professionals must achieve a level of comfort with suicide risk assessment that facilitates routine evaluation and prompt response in the case of a crisis as an integral part of optimizing care for the cancer patient.

Agitation

Whether agitation develops gradually or suddenly, witnessing a patient lose behavioral control is alarming to staff, family, and neighboring patients. Pacing, pulling out lines and tubes, becoming increasingly demanding or threatening, and combative behavior are examples of agitation that quickly draw the attention of medical staff and require immediate risk assessment and intervention. The safety of the patient and others in his or her vicinity is of chief concern, and a team consisting of nursing, medical, psychiatric, and security staff is most effective in quelling a dangerous situation.

Table 13.1 Initial strategies in calming the agitated patient

• Talk to the patient in a nonthreatening tone
• Allow the patient to express fears and concerns
• Isolate the patient from other patients and visitors
• Remove dangerous objects from the patient's vicinity
• Identify staff familiar with the patient and who the patient trusts
• Ask staff who are the target of patient's complaints and paranoia to leave the area
• Determine whether visitors are calming or agitating the patient
• Gather medical, psychiatric, substance abuse, and violence history
• Offer the patient a choice of voluntarily taking sedative medication before administering it intramuscularly or intravenously
• Offer the patient a choice of returning to the room voluntarily before using security restraints

Adapted from Roth AJ, Levenson JA. Psychiatric emergencies. In: Holland JC, Greenberg DB, Hughes MK, eds. Quick Reference for Oncology Clinicians: The Psychiatric and Psychological Dimensions of Cancer Symptom Management. Charlottesville, VA: IPOS Press; 2006. With permission from American Psychosocial Oncology Society (APOS)

Initial Strategies for Managing the Agitated Patient

Talk to the patient in a nonthreatening tone and allow the patient to express concerns. The patient may not make sense or may speak of persecutory delusions, but arguing with the patient should be avoided in the acute situation. Identify staff familiar with the patient and whom the patient trusts. Any staff member who is the subject of the patient's paranoia, even mistakenly, should be asked to temporarily leave the area for the sake of safety and de-escalation. Similarly, evaluate whether visitors are helpful in calming the patient or are causing further agitation. The patient should be quickly isolated from other patients in a quiet room or area. Any potentially dangerous objects should be removed from the area. Staff should be positioned in a manner that allows for a quick exit if the situation escalates to violence, and the patient should not be cornered against a window. Constant observation is essential until the situation is completely resolved (Table 13.1).

In the meantime, key information can be gathered from collateral sources or the patient's medical record, including medical status, timeline of mental status changes, psychiatric and substance abuse history, and agitation, violence, or suicidality history. Before restraining the patient or administering a sedative medication intramuscularly or intravenously, the patient should be offered the choice to return to his or her room or take the medication voluntarily. The use of physical restraints and sedatives is discussed below. Reassure family members and provide education to minimize distress. After a psychiatric emergency, gathering the staff and processing the experience to learn from it, venting emotions, and providing support to the team are helpful.

Causes

A key principle in evaluating altered mental status and agitation in the oncology setting is to first assume a medical etiology. Only after a medical cause is ruled out according to history and evaluation should behavioral changes be attributed to an underlying primary psychiatric illness. This approach avoids missing a medical condition presenting with psychiatric symptoms that may otherwise evolve into a medical emergency.

Agitation in the oncology setting is discussed below in four main categories.

1. Delirium, which results from the medical condition itself, medical complications, or medical treatments.
2. Adverse medication effects that produce agitation without a full-blown delirium episode.
3. Substance intoxication and withdrawal syndromes.
4. Exacerbation of primary psychiatric disorders, including depression, anxiety, mania, and psychosis.

Delirium

Delirium is a very common complication in the oncology setting. Although classified here as a psychiatric emergency, it more accurately represents a psychiatric manifestation of a medical emergency. The cause of delirium is one or more physiologic disturbances induced by medical conditions and/or medications, and the treatment requires medical evaluation and intervention. The psychiatric, cognitive, and behavioral symptoms must be managed simultaneously.

Delirium is sometimes referred to as altered mental status or encephalopathy. By definition, delirium is reversible upon resolution of underlying medical factors. This contrasts with dementia, a chronically progressive, irreversible cognitive disorder.

The prevalence of delirium in cancer patients is reported to range from 5 % to 30 %, and in terminally ill patients, it may be as high as 40–85 % (Fleishman et al. 1993). Patients with advanced cancer have an increased risk of delirium with the increased severity of their illness. In a prospective study of patients admitted to inpatient palliative care units, physicians diagnosed delirium in 40 % of patients at admission, and it developed in 45 % of the remaining patients (Lawlor et al. 2000a). Delirium also occurs in up to half of older patients postoperatively (Inouye 2006).

Delirium carries numerous potential costs in terms of morbidity and mortality. Beyond the immediate safety concerns of agitation and combativeness, delirium in elderly hospitalized patients is associated with a 22–76 % death rate during hospitalization. Up to 25 % of patients with delirium die within 6 months after discharge (Trzepacz et al. 2004). In some patients, baseline cognition may never return after an episode of delirium, with spouses describing that patients were “never quite the same again.” In addition, delirium is associated with increased lengths of stay and costs per day in the hospital. Patients with episodes of delirium during acute hospitalization have an increased likelihood of requiring discharge to a nursing facility or rehabilitation center.

Delirium can be emotionally traumatic for patients and their families. Roughly half of patients who experience delirium will remember aspects of their episodes (Breitbart et al. 2002). Patients who experience paranoid delusions or vivid hallucinations may have posttraumatic-like symptoms after the delirium clears. Loved ones who witness episodes may remain scarred by images of the patients losing control of their faculties.

Clinical Features

Delirium evolves acutely or subacutely, generally in hours to days. Symptoms fluctuate within each 24-hour period, with a typical waxing-waning course. Patients with delirium exhibit alterations in their level of arousal, ranging from lethargy to hyperactive/agitated. Attention is impaired, as evidenced by distractibility, the need for the examiner to repeat questions, and inability to shift focus to the appropriate stimulus. At least one cognitive deficit can be identified. The patient may become disoriented regarding time, place, and situation, but this is not a prerequisite for a diagnosis of delirium. Memory and language deficits are often apparent, and the patient's speech may become disorganized and nonsensical (Table 13.2).

Patients with delirium generally have abnormalities in the sleep-wake cycle. For instance, a patient may sleep throughout the day and stay awake only at night. Some of the most dramatic presentations of delirium involve perceptual disturbances. Hallucinating patients may describe animals in the room, furniture floating, or patterns and shapes on the walls. Tactile and auditory hallucinations are not uncommon, and a patient may experience paranoid delusions in response to these altered perceptions. Family members can often recall subtle changes in mood preceding acute presentation; these subclinical syndromes may follow episodes, as well. During an acute episode, the patient may be tearful and emotionally labile. Hypoactive delirium is often mistaken for depression.

Subtypes

Researchers have described three subtypes of delirium based on level of arousal: hyperactive, hypoactive, and mixed. Patients with hyperactive delirium are seldom overlooked, as they tend to become agitated and restless, frequently wandering the unit or trying to get out of bed without assistance. Their speech may become loud, and they can be seen responding to hallucinations. When staff members attempt to redirect or restrain hyperactive delirious patients, they may be uncooperative or even aggressive. These patients are at risk for harming themselves by falling or pulling out needed lines.

Patients with hypoactive delirium appear to be apathetic and withdrawn. Engagement in activities and oral intake are reduced, and the patient spends the day falling in and out of sleep. This listlessness may be misinterpreted as depression, but upon closer examination, cognitive and attentional deficits are present. These patients are at risk for self-harm owing to malnutrition, deconditioning, and passive refusal of medical interventions. Peterson et al. (2006) found that among patients

Table 13.2 Clinical features of delirium

Level of arousal and psychomotor activity
• Reduced awareness of environment
• Lethargy
• Hyperactivity/agitation
Inattention
• Inability to sustain attention
• Distractibility
• Inability to shift focus
Temporal course
• Acute or subacute onset
• Fluctuation of symptoms
Cognitive disturbance
• Memory impairment
• Disorientation
• Aphasia
• Apraxia
• Dysnomia
• Dysgraphia
Psychiatric symptoms
• Hallucinations
• Incoherent speech
• Mood lability
• Thought disorganization
• Anxiety
• Irritability
Sleep-wake cycle disturbance

Adapted from Breitbart W, Alici Y. Delirium. In: Holland JC, Breitbart W, Jacobsen PB, Lederberg MS, Loscalzo MJ, McCorkle R, eds. Psycho-Oncology. 2nd ed. New York, NY: Oxford University Press; 2010:332–339. With permission from Oxford University Press

admitted to an intensive care unit, those over the age of 65 years were twice as likely to have hypoactive delirium than were younger patients. This subtype carries a higher mortality risk than does hyperactive delirium.

The mixed subtype refers to presentations alternating between hyperactive and hypoactive.

Pathophysiologic Mechanism of Delirium

Understanding the mechanism underlying the development of delirium is helpful when examining specific etiologies. In essence, delirium results from decreased oxygen availability to the brain. This can result from decreased oxygen supply to the brain, such as in hypoperfusion, or increased oxygen demand, such as with

illness or surgery. Inadequate oxidative metabolism causes cortical depression owing to the inability of neurons to maintain ionic gradients and eliminate neurotoxic byproducts (Maldonado 2008).

Neuronal dysfunction causes dysregulation of neurotransmitters, thereby precipitating delirium. Specifically, a reduction in cholinergic activity (and corresponding increase in dopaminergic activity) and heightened GABAergic activity in the brain are thought to underlie the development of delirium. The acetylcholine-dopamine imbalance hypothesis is supported by the fact that anticholinergic medications are frequent culprits for delirium as well as by the use of dopamine-blocking antipsychotics in its management. Changes in serotonergic, glutamatergic, and opioidergic activity are implicated in the pathogenesis of delirium, as are cytokines. Overall, high cortical function is impaired by numerous interacting neurotransmitter systems and neuronal pathways.

Etiology

Researchers have compiled extensive lists of medical conditions and prescription drugs that cause delirium, and referencing them is useful when searching for the cause of altered mental status in a patient (Table 13.3). An important concept to

Table 13.3 Etiologies of delirium in cancer patients

Medications
• Anticholinergics
• Sedative hypnotics
• Opiates
• Chemotherapeutic agents
• Immunosuppressants
• Immunomodulators
• Antiemetics
• Corticosteroids
• Serotonin syndrome
Substance intoxication or withdrawal
• Alcohol intoxication
• Alcohol withdrawal
• Sedative hypnotic intoxication
• Sedative hypnotic withdrawal
• Amphetamines
• Cocaine
• Hallucinogens
Metabolic
• Volume depletion or overload
• Acidosis or alkalosis

(continued)

Table 13.3 (contined)

• Uremia
• Anemia
• Hepatic failure
• Hypoglycemia or hyperglycemia
• Hypoalbuminemia
• Electrolyte abnormalities
• Thyroid storm
• Hypopituitarism
Hypoxia
• Pulmonary insufficiency
• Pulmonary emboli
• Cardiac failure
Neoplastic disease
• Primary CNS tumor
• Metastatic CNS tumor
• Leptomeningeal disease
• Paraneoplastic syndrome
CNS infection
• Meningitis
• Encephalitis
• Abscess
• Human immunodeficiency virus
• Neurosyphilis
Systemic infection
• Bacteremia/sepsis
• Fungal
• Viral
• Protozoal
Cerebrovascular
• Stroke
• Seizures
• Hypertensive encephalopathy
• Subarachnoid hemorrhage
• Subdural hematoma
• Cerebral edema
Other
• Radiation
• Postoperative state
• Disseminated intravascular coagulation and other hypercoagulable states
• Hematologic abnormalities

Adapted from Trzepacz PT, Meagher DJ. Delirium. In: Levenson JL, ed. Textbook of Psychosomatic Medicine. Washington, DC: American Psychiatric Publishing; 2005:91–130. With permission from American Psychiatric Publishing, Inc.

keep in mind is that delirium is usually multifactorial. Therefore, a seemingly minor medical complication or normal medication dose can cause changes in sensorium in a cumulative manner. For example, a patient continuing to take a usual home regimen of an opiate analgesic may be tipped into delirium when admitted to the hospital for pneumonia.

Risk Factors for Delirium in Cancer Patients

Cancer patients have characteristics that are risk factors for delirium. Cancer rates increase with age, as does the prevalence of cognitive impairment and dementia. Underlying dementia is a well-established risk factor for delirium. Elderly patients may have mild cognitive impairment or pre-existing dementia at baseline, thereby increasing their risk of delirium when acutely ill. Substance abuse and dependence—specifically, alcohol and tobacco—are risk factors for certain types of cancer. Patients abusing these substances are also at risk for intoxication or withdrawal syndromes, resulting in agitation and/or altered mental status.

Cancer patients are particularly vulnerable to delirium at certain junctures of their disease. The perioperative period poses risks because of anesthesia, the physical trauma of the surgery itself, shifts in fluid and electrolyte level, pain, use of opiate analgesics, and complications including wound infection, urinary tract infection, pneumonia, anemia, autonomic instability, and hypoxia.

Hospitalization is frequently required at various time points in the patient's illness. This poses numerous risks for the development of delirium in addition to the medical situation necessitating hospitalization. These include a change in environment, lack of access to substances of abuse (precipitating withdrawal syndrome), sensory impairment (if access to glasses or hearing aids is restricted), sleep deprivation, polypharmacy, and use of intravenous (IV) lines, bladder catheters, and physical restraints.

Certain cancer treatments may place the patient at increased risk for delirium. Intrathecal chemotherapy and whole-brain irradiation are examples. Immunosuppressants, including tacrolimus and mycophenolate, can directly cause delirium via neurotoxicity, and they increase the risk of central nervous system (CNS) infections in patients presenting with altered mental status. Some chemotherapeutic agents, including methotrexate, cytarabine, fluorouracil, vincristine, vinblastine, bleomycin, bis-chloronitrosurea, cis-platinum, ifosfamide, asparaginase, and procarbazine, can cause mental status changes. Immunotherapeutics such as high-dose interleukin and interferon also are associated with delirium.

In the terminal stages of cancer, delirium typically manifests in the final days. One study found delirium to be present in 88 % of patients at least 6 h before death (Lawlor et al. 2000a).

Many types of cancer have CNS involvement, for example, primary and metastatic brain tumors and leptomeningeal carcinomatosis. Altered mental status may stem from the direct effects of these diseases or secondary seizures. Paraneoplastic syndromes occur when a tumor produces substances that cause remote effects at a distance from it. The paraneoplastic syndrome encephalopathy is most commonly associated with squamous cell lung cancer and breast cancer.

Workup

Medical history will reveal the acute or subacute temporal course of mental status changes, which helps distinguish delirium from dementia and underlying chronic psychiatric illnesses. Baseline cognitive status is key to the differential. A history of substance abuse is an important component of the evaluation, and collateral sources of information may be required. In addition, a complete medication list and any recent changes provide valuable clues about delirium. Upon physical examination, the clinician may find signs of a medical condition or systemic signs of medication side effects. Mental status testing, particularly the cognitive examination, is essential to the diagnosis of delirium.

Structured instruments are available for screening and monitoring delirium. The Memorial Delirium Assessment Scale measures the severity of delirium and is designed to be repeated throughout the day to monitor treatment response (Lawlor et al. 2000b). It is quite useful as a screening tool, and researchers have validated it in hospitalized patients with advanced cancer. The Delirium Rating Scale-Revised-98 is another useful instrument for rating delirium severity (Trzepacz et al. 2001). The Confusion Assessment Method has been simplified into a 4-item screen for delirium (Inouye et al. 1990). It has lower sensitivity and specificity than the Memorial Delirium Assessment Scale and Delirium Rating Scale-Revised-98, but it can be administered by nonpsychiatrists.

Laboratory workup for delirium is based on clinical suspicion of the underlying etiology. This includes complete blood count; measurement of electrolytes, blood urea nitrogen/creatinine, glucose, thyroid-stimulating hormone, vitamin B_{12}, folate, arterial blood gas, and serum drug levels; liver function tests; urine drug screening; urinalysis; electrocardiography; and a chest X-ray. Brain imaging (computed tomography and magnetic resonance imaging) and lumbar puncture are frequently indicated in the cancer population for the differential diagnoses discussed in detail above, including for brain tumors, stroke, intracranial bleeding, CNS infection, and leptomeningeal disease. Electroencephalography not only assesses patients for seizures but also shows generalized slowing in the dominant posterior rhythm in 81 % of delirium cases. In contrast, it reveals diffuse slowing in 33 % of dementia cases, and these changes generally occur only at during the latter stages of dementia (Jacobson and Jerrier 2000).

Treatment

Treatment of delirium requires identification of the underlying cause and implementation of appropriate medical intervention. Potential medical etiologies and appropriate workup are discussed above. If the altered mental status is thought to be medication-induced, discontinue or minimize the use of deliriogenic medications. If safe, effective alternatives exist, switching medications is indicated. Benzodiazepines and anticholinergics should be tapered and avoided (unless the etiology is alcohol or benzodiazepine withdrawal). With opiate pain medications, a balance must be

achieved between their delirium-exacerbating potential and the risk of uncontrolled pain causing agitation. Opiate pain medications can be rotated, and use of meperidine should be avoided owing to high rates of neurotoxicity. Potential interactions that affect the pharmacokinetics or clinical effects of a drug should be identified. This can be done conveniently and quickly using one of many available online drug interaction programs.

Nonpharmacologic Management

During the search for the medical etiology of delirium, behavioral and cognitive symptoms must be managed. In fact, even after treatment of the medical problem and eliminating deliriogenic medications, symptoms of delirium can persist for an indefinite period.

Safety concerns should be addressed first. Tips for calming an agitated patient are described above. A one-to-one sitter may be required for constant redirection and supervision. Fall precautions should be instituted, and the medical staff must be made aware of the change in mental status. The patient should be moved to a room closer to the nursing station, and dangerous objects should be removed from the room. In extreme cases of agitation when a patient is at risk for self-harm, violence toward other patients, or pulling out essential medical devices, physical restraints may be necessary. Because this intervention can exacerbate agitation, frequent attempts to remove restraints should be made, especially as other management strategies are instituted.

Nonpharmacologic strategies are very helpful in both the prevention and management of delirium. Correct malnutrition, dehydration, and electrolyte abnormalities. Supplement oxygen delivery and remove immobilizing lines such as bladder catheters, IV lines, and drains as soon as possible. Make glasses and hearing aids available to the patient to prevent sensory deprivation and disorientation. Ensure bladder and bowel function. Light (e.g., windows) and noise (e.g., music, television) can be used to promote a normal sleep-wake cycle. Minimize nighttime awakening by staff. Reduce environmental isolation by encouraging family presence, frequent staff visits, or use of a one-to-one sitter. Frequent reorientation and prominent display of cues such as a clock, a calendar, and location signs are helpful for the confused patient.

Avoid the use of physical restraints, as it may exacerbate agitation. Restraints are sometimes necessary to prevent self-harm when less restrictive alternatives are unavailable, but frequent attempts to remove restraints should be made. Two-point arm restraints, four-point arm and leg restraints, lap belts, and Posey vests are types of physical restraints. Mitts can be helpful in preventing patients from pulling out IV lines and drainage tubes. Knowledge of institutional policies regarding the use of physical restraints as well as monitoring and order requirements is important. Of note, cancer patients should be restrained carefully owing to risk of fractures, and prolonged immobilization increases their risk of clots.

Pharmacologic Management

The goal of medical intervention for delirium is to calm the patient while maintaining arousal and ability to communicate. Chemical restraint refers to using psychotropics to sedate patients and keep them quiet. This is not an appropriate management goal. In terminally ill patients, the focus is on providing comfort; level of arousal is sometimes affected in this population.

Antipsychotics represent the pharmacologic treatment of choice for delirium. Although prescribed more commonly to control agitation, both haloperidol and chlorpromazine are effective in improving symptoms and cognitive function in patients with hypoactive delirium (Breitbart et al. 1996). Benzodiazepines may actually worsen confusion, predispose a patient to falls, cause paradoxical disinhibition, and prolong the delirium episode. Lorazepam is used in combination with haloperidol (0.5–2.0 mg intravenously) if haloperidol does not calm the patient (see below), but it should not be given alone. However, as described below, benzodiazepines represent the mainstay of therapy in cases of alcohol withdrawal. Diphenhydramine has sedative properties, but it should not be administered to calm an agitated, confused patient owing to its significant anticholinergic activity, which exacerbates delirium.

No medications are approved by the U.S. Food and Drug Administration for the management of delirium. Head-to-head clinical trials comparing the efficacy of different antipsychotics for delirium have been limited. Therefore, choosing an antipsychotic depends on the route of administration, level of sedation required, and side effect profile (Table 13.4). Of note is that elderly and frail patients require lower doses than do younger, stronger patients.

Haloperidol remains the first-line antipsychotic for the management of delirium in the medical setting. Begin at a low dose (0.5–2.0 mg intravenously) and repeat every 30–60 min until agitation begins to decrease. Haloperidol can be administered intravenously or intramuscularly; however, the parenteral route of administration is twice as potent as the oral route, so the dose should be adjusted accordingly. Platelet counts and coagulation parameters should be considered prior to administering medications intramuscularly owing to risk of hematoma.

Many antipsychotics, particularly IV haloperidol, can prolong the corrected QT (QTc) interval, predisposing the patient to torsades de pointes. Therefore, baseline electrocardiography and subsequent regular monitoring of the QTc interval are indicated. Also, levels of electrolytes, particularly potassium and magnesium, should be monitored. Check the medication list for other QTc-prolonging drugs and assess the patient for other torsades de pointes risk factors. Vital signs should be monitored closely, as well.

Typical antipsychotics such as haloperidol carry a higher risk of extrapyramidal symptoms than do atypical antipsychotics (see below); these symptoms include tremor, rigidity, akathisia, and acute dystonia. Acute dystonia can occur upon initial administration of haloperidol or when the dose is increased. This is defined as involuntary, sustained contraction of muscles, usually of the trunk, limbs, or neck. Parenteral administration of diphenhydramine or benztropine is the treatment of choice when

Table 13.4 Antipsychotic management of delirium

Medication	Dose range	Route of administration	Level of sedation	Side effects
Haloperidol	0.5–2.0 mg every 2–12 h	PO,[a] IV, IM	Low	Monitor QTc interval on EKG, extrapyramidal side effects, IM/IV twice as potent as PO
Chlorpromazine	10–50 mg every 4–6 h	PO,[a] IV, IM, PR	Very high	Orthostatic hypotension, anticholinergic side effects, IM/IV four times as potent as PO
Risperidone	0.25–1.00 mg every 12–24 h	PO[a,b]	Low	Extrapyramidal symptoms at high dose ranges, orthostatic hypotension
Olanzapine	2.5–5.0 mg every 12–24 h	PO,[b] IM	High	Orthostatic hypotension, anticholinergic side effects
Quetiapine	12.5–100.00 mg every 12–24 h	PO	High	Orthostatic hypotension, anticholinergic side effects
Ziprasidone	10–40 mg every 12–24 h	PO, IM	Low	Monitor QTc interval on EKG, IM twice as potent as PO
Aripiprazole	5–30 mg every 24 h	PO,[a,b] IM	Very low	May cause akathisia

Adapted from Breitbart W, Alici Y. Delirium. In: Holland JC, Breitbart W, Jacobsen PB, Lederberg MS, Loscalzo MJ, McCorkle R, eds. Psycho-Oncology. 2nd ed. New York, NY: Oxford University Press; 2010:332–339. With permission from Oxford University Press

PO per oral, *EKG* electrocardiogram, *PR* per rectum

[a]Oral solution

[b]Oral disintegrating tablet

this occurs. If the patient exhibits an increase in agitation following administration of haloperidol, akathisia may be a concern. This extrapyramidal side effect is an intense subjective sense of restlessness resulting in an inability to sit still comfortably. This can be managed with propranolol or a benzodiazepine. In the case of any extrapyramidal adverse effect, switching to an atypical antipsychotic is indicated.

Chlorpromazine can be considered if haloperidol, haloperidol plus lorazepam, or a sedating atypical antipsychotic is not effective in calming the patient. It must be used with caution owing to cardiovascular, hypotensive, and anticholinergic side effects.

Atypical antipsychotics are also used in the management of delirium, although less commonly, with selected antipsychotics shown to be effective. No atypical antipsychotics are available in an IV formulation. Physicians have accumulated more clinical experience in the context of delirium management with risperidone, quetiapine, and olanzapine than with the other atypical antipsychotics. Advantages of these medications include less QTc prolongation than with IV haloperidol (least

with olanzapine), reduced incidence of extrapyramidal symptoms (with the exception of high-dose risperidone), and reduced level of sedation.

Long-term use of atypical antipsychotics, particularly risperidone, quetiapine, and olanzapine, is associated with potentially dangerous side effects, including weight gain, hyperlipidemia, high blood pressure, diabetes mellitus, cardiovascular disease, and metabolic syndrome. Therefore, these medications should be tapered and discontinued once the episode has resolved and not inadvertently left on the patient's medication list. The U.S. Food and Drug Administration issued a warning regarding increased risk of death for both typical and atypical antipsychotics in elderly patients with dementia-related psychosis. Of note, several antipsychotics also possess antiemetic properties, particularly haloperidol, chlorpromazine, and olanzapine, which can be of added benefit in cancer patients.

Experience with ziprasidone and aripiprazole is limited in the medical setting. These atypical antipsychotics have a lower risk of metabolic syndrome and are less sedating than other antipsychotics. Physicians have primarily used ziprasidone in an intramuscular (IM) formulation as an acute sedative, but caution is advised owing to risk of QTc prolongation, bradycardia, and orthostasis. Aripiprazole is the least sedating atypical antipsychotic used in medically ill patients and may even be stimulating. Recent studies indicated that this medication may be useful, particularly against hypoactive delirium. Clozapine is not used in cancer patients owing to a risk of agranulocytosis and decreased seizure threshold.

Dexmedetomidine is an α-2-adrenergic receptor agonist used for brief intraoperative sedation. It has been used in the intensive care unit setting for conscious sedation in agitated patients not tolerating or responding to antipsychotics. Dexmedetomidine has a short half-life, and the risk of exacerbating delirium with it is likely lower than that with other sedatives. However, hypotension is common in patients receiving it, and constant monitoring of vital signs is required with its use.

Adverse Effects of Medications

Certain medications used in cancer patients cause psychiatric side effects presenting as agitation short of precipitating full-blown delirium episodes.

Antiemetics

Akathisia, described above in the context of extrapyramidal symptoms due to antipsychotics, causes a subjective feeling of restlessness and inability to sit still. Clinical manifestations include pacing and insomnia, and the patient describes the feeling as anxiety or "losing control." In cancer patients, antiemetics are common causes of medication-induced akathisia. Included on the list are metoclopramide, promethazine, and prochlorperazine. Management of akathisia involves switching to another antiemetic, such as ondansetron or lorazepam, and brief treatment with propranolol or a benzodiazepine until it subsides.

Corticosteroids, Immunosuppressants, and Immunomodulators

Corticosteroids also have psychiatric side effects. At low chronic doses, depression is common. At high acute doses, agitation, akathisia, mania, and psychosis can occur. Other immunosuppressants, such as tacrolimus and mycophenolate, are prone to causing irritability, anxiety, and agitation. Although immunotherapeutic agents such as interferon-α and interleukin-2 are more likely to precipitate depression, they are also associated with agitation and mania. Agitation is treated effectively with benzodiazepines and atypical antipsychotics.

Serotonin Syndrome

Both procarbazine, an antineoplastic agent, and linezolid, an antibiotic, possess monoamine oxidase-inhibition properties. Therefore, co-administration of antidepressants with these medications is contraindicated owing to the potential for serotonin syndrome. This is a potentially fatal syndrome, symptoms of which include autonomic instability, muscle rigidity, tremor, clonus, diaphoresis, altered mental status, and hyperreflexia. Tramadol and cyclobenzaprine are also implicated in causing serotonin syndrome when combined with monoamine oxidase inhibitors.

Psychotropics

Use of certain mood stabilizers and antidepressants requires serum-level monitoring and can cause mental status changes at toxic levels. For example, lithium levels are sensitive to dehydration, renal insufficiency, and medication interactions. Also, valproate and carbamazepine can cause altered mental status at supratherapeutic levels, as can tricyclic antidepressants.

Benzodiazepines may cause paradoxical disinhibition, especially in patients with brain tumors associated with cognitive impairment. Psychiatric medications are largely metabolized by the hepatic cytochrome P450 system. As a general rule, checking the drug interaction profile before starting any psychiatric medication to avoid adverse effects or changes in serum levels of medications with narrow therapeutic indices is wise. Levetiracetam is frequently prescribed for seizure prophylaxis in patients with CNS pathology, and its use has been associated with depression, irritability, and agitation.

Substance Intoxication and Withdrawal

Alcohol, Benzodiazepines, and Barbiturates

Patients with alcohol use disorders can present with agitation when intoxicated or during withdrawal. Upon being diagnosed with cancer, alcohol-dependent patients commonly stop drinking “cold turkey,” precipitating withdrawal. On each occasion

the patient is hospitalized, the risk for withdrawal begins as soon as a few hours after the last drink. Of note, the postoperative signs of alcohol withdrawal may be delayed owing to use of benzodiazepines for anesthesia and sedation.

Benzodiazepines and barbiturates are similar to alcohol in terms of intoxication and withdrawal syndromes. Increasingly, the benzodiazepine alprazolam is available illegally, referred to as "bars." Given its short half-life and propensity for misuse, alprazolam is associated with a particularly severe withdrawal syndrome. Even patients using benzodiazepines and barbiturates as prescribed are at risk for withdrawal syndrome in the hospital if the medications are not continued or dosages are decreased.

Alcohol, benzodiazepine, and barbiturate withdrawal can be fatal. Early signs of withdrawal include tremulousness, diaphoresis, nausea, vomiting, diarrhea, anxiety, insomnia, and restlessness. These symptoms may occur soon after the last drink or dose depending on the half-life of the substance. In severe cases, autonomic hyperactivity/dysfunction and hallucinations develop. If left untreated, withdrawal can progress to seizures and, ultimately, delirium tremens within 72–96 h (with long-acting benzodiazepines, onset may be delayed). Delirium tremens is a type of delirium marked by incoherence, psychosis, and agitation that occurs in about 15 % of alcohol-dependent patients during withdrawal.

Treatment of alcohol, benzodiazepine, and barbiturate withdrawal involves benzodiazepine use and tapering. Typically, lorazepam is used in the oncologic setting because it can be administered intravenously or intramuscularly at the same potency as when it is given orally, and it does not require phase 1 hepatic oxidative metabolism. Dosing starts at 0.5–2.0 mg every 1–6 h depending on the baseline level of substance use. Once symptoms are stabilized, the benzodiazepine should be slowly tapered over several days. If delirium or agitation becomes an issue in the context of withdrawal, antipsychotics are effective in the management of behavioral disturbances when given in conjunction with lorazepam. IV hydration, a vitamin-mineral solution, thiamine, and folate also should be given because of the incidence of malnutrition in this population and risk of Korsakoff syndrome.

Narcotic Analgesics

Pain is a common symptom in cancer patients, and opiates remain the mainstay of pain treatment. Patients taking chronic pain regimens often become physically dependent on narcotics, and they are at risk for withdrawal syndrome if their medications are discontinued or doses are significantly decreased. Signs and symptoms of opiate withdrawal include muscle aches, rhinorrhea, lacrimation, dilated pupils, nausea, vomiting, diarrhea, yawning, fever, insomnia, and dysphoric mood. Agitation, restlessness, and insomnia become factors, particularly when underlying pain is uncontrolled and adds to the discomfort of the withdrawal syndrome.

Treatment of narcotic analgesic withdrawal involves careful assessment of the patient's home regimen and reinstitution of pain medications. If the patient has been

using narcotics inappropriately, taper them to appropriate doses with the help of antidiarrheals, diphenhydramine, and nonnarcotic pain medications for withdrawal symptoms. Ascertaining the doses of opiates that are appropriate in this population can be difficult, and a referral to a pain specialist may be quite helpful. Patients with a history of nonprescription opiate abuse and dependence may experience pain syndromes in the context of a cancer diagnosis. Higher than usual doses may be necessary to treat pain in this population owing to tolerance, and use of these doses while monitoring for suspicion of misuse is appropriate. A history of opiate abuse is not a contraindication for use of narcotic analgesics by cancer patients, and agitation may ensue if pain is inadequately controlled.

Recreational Drugs

Although beyond the scope of this chapter, bearing in mind that cancer patients abuse recreational drugs and can present to the emergency room with agitation is important. These drugs include cocaine, methamphetamine, 3,4-methylenedioxy-*N*-methylamphetamine, and phencyclidine. Medical history and urine drug screening are helpful in diagnosing agitation in this population, and use of benzodiazepines and antipsychotics is indicated for cases of acute agitation.

Primary Psychiatric Disorders

Exacerbation of primary and underlying psychiatric disorders can precipitate emergencies in the oncology setting. In this section, common psychiatric conditions that manifest as agitation are briefly reviewed. Specific interventions are not discussed; instead, psychiatric conditions are described to aid the clinician in formulating a differential diagnosis when evaluating an agitated patient in an emergency setting.

Depression

Depression is common in cancer patients and may be a normal reaction to difficult circumstances, psychiatric manifestation of cancer or its treatment, or primary disorder.

A major depressive episode is defined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* as at least a 2-week period of depressed mood or loss of interest or pleasure occurring in the presence of other symptoms, such as sleep or appetite disturbance, low energy, poor concentration or indecisiveness, feelings of guilt or worthlessness, and recurrent thoughts of death or suicide. Suicidal ideation is a true psychiatric emergency and is discussed in detail below. However, severe irritability, decrease in oral intake (especially in elderly patients), and depression-related psychosis can result in the need for urgent clinical intervention.

Emotional support and empathic listening can be extremely helpful to the depressed cancer patient. If the presenting patient is experiencing suicidality, psychosis, or malnutrition/dehydration, a psychiatric consultation is warranted to complete a risk assessment to determine whether the patient needs a higher level of psychiatric care, such as inpatient psychiatric hospitalization. Urgent prescription of antidepressants generally is not needed because the usual onset of action is 4–6 weeks. Psychostimulants such as methylphenidate have more immediate results than do antidepressants in terms of mood, energy, and appetite, and this intervention is useful in depressed, cachectic cancer patients. Such patients should undergo careful cognitive screening to rule out hypoactive delirium.

Anxiety

Anxiety and worry are typical parts of the cancer experience owing to loss of control and uncertainty. The looming threat of pain and death can create panic and fear. As with depression, anxiety may be a normal reaction to difficult circumstances, psychiatric manifestation of cancer or its treatment, or primary anxiety disorder.

In psychiatry, anxiety disorders are subdivided into several different diagnostic categories, including generalized anxiety disorder, panic disorder, agoraphobia, specific phobias (fears of injections, transfusions, and medical care are specified as subtypes), separation anxiety disorder, social anxiety disorder, anxiety owing to another medical condition, and substance/medication-induced anxiety. Trauma- and stressor-related disorders include posttraumatic stress disorder and adjustment disorders, both of which are quite prevalent in cancer patients. In the oncology setting, many factors may contribute to anxiety and fear. Panic attacks, specific phobias, anticipatory anxiety, and posttraumatic stress disorder are most likely to precipitate an emergency.

A panic attack is a period of intense fear or discomfort accompanied by symptoms such as shortness of breath, chest pain and palpitations, diaphoresis, tremor, dizziness, hot flashes or chills, nausea, and fear of losing control or dying. These symptoms occur together and achieve peak intensity within 10 min. Clinicians must be careful to exclude medical causes of these symptoms before attributing them to panic attacks.

Claustrophobia becomes an issue when magnetic resonance imaging is performed or during isolation due to infection. Radiation and needle fears are potentially detrimental health-related phobias. Patients may avoid essential cancer workup and treatment because of anxiety, and staff members may need to intervene when a patient undergoing a procedure has a panic attack.

Similarly, anticipatory anxiety can be quite severe prior to administration of chemotherapy or surgery. Patients often have panic attacks as well as generalized anxiety in anticipation of recurrence screening appointments or while awaiting test results.

Posttraumatic stress disorder is defined as a combination of symptoms occurring after a person faces a life-threatening situation, serious injury, or sexual violence.

These symptoms are categorized as intrusion, avoidance, hyperarousal, and negative alterations in cognition and mood. The feelings of vulnerability brought about by cancer treatment and potential for adverse outcomes can cause a resurgence of these symptoms. Flashbacks and intense hypervigilance can manifest as agitation and may be mistaken for psychosis, anxiety, or medication side effects.

Ruling out medical conditions, such as endocrine abnormalities, uncontrolled pain or nausea, pulmonary embolism, and metabolic conditions, as causes of acute anxiety is important. Use of corticosteroids and antiemetics is associated with anxiety and restlessness, as well.

Support, validation, and education are essential initial steps in managing the anxious patient. Crisis intervention and cognitive-behavioral techniques can be used by mental health providers to calm patients. Benzodiazepines may be needed for their immediate anxiolytic effect. Lorazepam is most commonly used in the medical setting owing to its rapid onset of effects, potential for IV administration, and preference in patients with liver disease. The patient should be warned of medication side effects, including incoordination and sedation, to prevent falls and accidents. Also, addictive potential is an important factor to consider in patients with a history of substance dependence needing long-term anxiety control. Respiratory depression and risk of confusion may prohibit the use of benzodiazepines in certain patients. Sedating atypical antipsychotics such as olanzapine and quetiapine may be useful for acute anxiety as well as concomitant insomnia. Serotonergic antidepressants and buspirone are used for long-term treatment of anxiety.

Mania

Mania is an elevated or irritable mood state occurring with bipolar disorder, but a medical cause must be ruled out in the manic cancer patient. Corticosteroid- and interferon-based therapy have been associated with mania and mixed states.

Mania is defined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* as at least 1 week of elevated or irritable mood and increased goal-directed behavior or energy accompanied by symptoms such as grandiosity, decreased need for sleep, racing thoughts, pressured speech, distractibility, and recklessness. Psychotic features also may be present, including delusions and hallucinations. The manic patient is at risk of harming himself or herself or others owing to disinhibition, impulsivity, delusional beliefs, and hyperactivity. Irritable mania can be marked by particular agitation and violence.

Agitation in patients with mania can be addressed using antipsychotics with or without lorazepam until psychiatric consultation. If the patient is taking a mood stabilizer such as lithium, valproate, or carbamazepine, serum drug levels should be checked. Ultimately, a risk assessment must be completed to determine whether the patient needs an increased level of psychiatric care, such as inpatient psychiatric hospitalization.

Psychosis

Schizophrenia and related disorders are psychiatric illnesses involving chronic delusions, hallucinations, disorganized speech and behavior, and negative symptoms. Exacerbation of these disorders can be difficult to differentiate from delirium. Interestingly, psychiatric illness can predispose individuals to delirium, further complicating the diagnosis.

Delusions are defined as false, fixed beliefs and are often persecutory in nature. In schizophrenic patients, the delusions tend to be more systematized and less fragmented than in delirious patients. Also, auditory hallucinations are most common with schizophrenia, whereas visual and tactile hallucinations are predominant with delirium. Disorganization of speech and behavior appear to be similar with schizophrenia and delirium, and the patients often appear confused. Cognitive examination in both types of patients may demonstrate attentional deficits, but orientation is generally unimpaired in patients with schizophrenia. In addition, decreased arousal is not present in patients with schizophrenia but is common in those with delirium. A temporal symptom course is key to differentiating schizophrenia from delirium.

Agitation owing to psychosis can be addressed using antipsychotics with or without lorazepam until a risk assessment can be completed to determine whether the patient needs an increased level of psychiatric care, such as psychiatric hospitalization.

Cancer and Suicidality

Prevalence of Suicide

About 1 million people worldwide commit suicide each year. Suicides are more common than homicides or deaths caused by acquired immunodeficiency syndrome in the United States. Suicide has multiple risk factors, including depression, anxiety, a history of other mental health disorders, substance abuse, recent loss of employment or relationship, and a general lack of social support (Table 13.5). Illnesses, specifically cancer, heighten the risk of suicide, with the number of suicides in cancer patients found to be 1.3–2.6 times higher than that in the general population

Table 13.5 Risk factors for suicide

Biological	Psychological	Social
Cancer	Hopelessness	Loss of employment
Mental illness	Depression	Loss of relationship
Medical illness	Substance dependence	Lack of social support
Male	Suffering	Recent death in family
Substance dependence	Anxiety	Past trauma
Older age or young adult	Impulsivity	Family suicide
Pain	“I am a burden”	Easy access to means

(Spoletini et al. 2011). A recent study of older Americans found that cancer was the only medical illness associated with suicide according to a multivariate analysis (Miller et al. 2008).

Risk Factors

Among cancer patients, those at highest risk include men and individuals with advanced disease, little social support, limited treatment options, or head and neck cancer (Spoletini et al. 2011). Other cancers that may increase suicide risk are those of the lung and stomach (Misono et al. 2008). Patients with diagnoses of metastatic prostate cancer have a relative risk 2.6 times greater than that in men without cancer in the first year following diagnosis (Van Leeuwen and Schroder 2010). However, all cancer patients have a higher risk of suicide than the general population. Depression is a factor in about half of all suicides (Pessin et al. 2010). Researchers have hypothesized that altered function of the immune system may predispose cancer patients to depression.

Depression

Patients may present with pre-existing depressive illness or experience symptoms of depression after a cancer diagnosis. Suicidal thoughts represent one symptom of depressive illness, and suicidal statements should always be taken seriously. A patient may have other symptoms of depression, including depressed mood, anhedonia, marked change in appetite (with more than 5 % weight loss or gain in 1 month), insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, trouble thinking or concentrating, and indecisiveness. If several of the above symptoms are present, assessment for a major depressive episode, including possible suicidal thinking, is reasonable. Because cancer patients may experience some of these symptoms owing to their cancer or its treatment, researchers have suggested alternative depression criteria for this population, although the symptoms published in the *Diagnostic and Statistical Manual of Mental Disorders* by the American Psychiatric Association remain the mainstay of diagnosis. The presence of other psychiatric diagnoses also heightens the risk of suicide, as does delirium and pre-existing psychosis. A previous suicide attempt or history of self-injurious behavior is an important red flag during evaluation and is associated with an increased risk of future suicidality.

Pain

In cancer patients, pain, particularly a high level of chronic pain that cannot be relieved, may lead to thoughts of suicide as a way to escape the pain. Patients with high pre-existing levels of depression or anxiety often experience a higher level of

pain than do those who are not extremely depressed or anxious. This may be caused in part by a low serotonin level changing the brain's ability to modulate pain signals received, resulting in the depressed or anxious patient's brain becoming more sensitized to any painful stimuli. Addressing both the physical cause of pain and psychiatric symptoms, if present, is important to reduce pain levels.

Times To Be Watchful

Individual patients react quite differently to diagnoses of cancer. Although this may depend in part on the severity of the diagnosis, it is also affected by the individual's personality and typical pattern of reacting to a crisis. Crisis points for potential suicidal thinking include the initial diagnosis and a few weeks afterward as well as news of a worsening illness or metastasis. News of a lack of available treatment options, which typically coincides with the approach to end-of-life care, can also precipitate psychological distress and increase the possibility of thoughts of suicide. Apparently, the suicide risk is high at every point in the cancer trajectory. Studies have found an increase in risk in the first 3–5 months after diagnosis as well as within 5 years of diagnosis and in patients with advanced cancer (Spoletini et al. 2011; Misono et al. 2008; Pessin et al. 2010). Some patients may entertain thoughts of suicide when they lose functional ability, for example, loss of the ability to walk owing to spinal metastasis. Some patients adjust relatively well to loss of independence and increasing dependence on providers, whereas for others, the realization of loss of ability to care for themselves can be emotionally devastating. This can be more of an issue for patients with a very limited or nonexistent social support network.

Evaluation of Suicidal Patients

Evaluation of the suicidal patient is critical in preventing loss of life. Although preventing every suicide attempt may be impossible, clinicians can usually see strong clues regarding how serious a patient may be about suicide and intent to follow through with an attempt. Many patients who commit suicide speak with health care providers within weeks or months before their deaths. Empathic listening, especially during crisis points in treatment, can alert the provider to a potentially suicidal patient. If symptoms of depression are present, asking the patient directly about thoughts of wanting to die is important. Asking about suicidal thoughts does not encourage a patient to commit suicide and may be the link to providing help, treatment of depression, and relief of distress.

Not all patients who express a wish to die are actively suicidal. Many think that something happening to cause them to die sooner rather than later would be preferable because of their physical or emotional pain or because they see their situations

as hopeless. Many patients talk about not wanting to prolong the suffering of family members who are caregivers or who feel close to them, as they are also affected emotionally by the illness. Patients not actively planning to harm themselves but wishing that death would come soon in some form are considered to have "passive" suicidal ideation. Patients with passive suicidal thoughts are not at extreme risk for suicide. They are having thoughts of death and may prefer to die soon but do not intend to hasten their death. These patients can still benefit from a thorough assessment for depressive symptoms and treatment recommendations.

In comparison, patients with "active" suicidal thoughts are at greater risk for suicide. These are people planning to harm themselves or who have recently thought of ways to kill themselves. An example is a patient who has thought of purposefully overdosing on opiate medications. Also of importance is the patient's own verbalized intent to harm himself or herself and any previous suicide attempts. Intent involves the person's degree of commitment to following through with suicidal thoughts. Some patients may say, "Well, I know that too much pain medication could kill me, but I would never do that. I love my family too much." This indicates that the patient has thought of a plan but is not intending to follow through with it. The patient still has a degree of risk and needs treatment but is likely not planning to act on suicidal thoughts imminently. Other patients may actually intend to follow through. A statement like "I might" or "I don't know" or simply silence when asked about this should result in further investigation. Some patients actually say they intend to commit suicide when able. The provider should also evaluate means of suicide, such as availability of medications for overdose or weapons, if a patient has a plan and/or intent to commit suicide. For example, if a patient admits to hoarding medications, this indicates a plan and action regarding that plan. Also, a patient who made a suicide attempt in the past is at high risk for making another attempt; a patient's history of suicide attempts should be obtained if he or she is having suicidal thoughts. Patients with a family history of suicide are also at increased risk. Anxiety or agitation and a history of poor impulse control is a dangerous combination when suicidal thoughts are present and should heighten attention to the patient's safety.

Many clinicians are understandably uncomfortable about questioning a patient about suicidal thoughts, as this is not an everyday conversation for medical personnel working in non-mental health-related fields. However, it can be approached in a calm, matter-of-fact way, and the clinician can become comfortable in discussing the subject. One way to bring up the subject of suicidal thinking is to normalize and indicate the reason for questioning. "Many people with (cancer, your cancer, in your situation) struggle with depression and may have thoughts about wanting to die. Have you had any thoughts like that?" is one way to begin the conversation. If the patient has had such thoughts, explore exactly what type of thoughts he or she has had. If the patient answers "not really," ask what "not really" means. He or she may be having suicidal thoughts of an active or passive nature. If the patient's safety appears to be at risk, questioning his or her family members is also important. Although normally the patient's permission is obtained to include others in a psychiatric discussion regarding the patient, when the patient is suspected of being

suicidal, obtaining this permission is not necessary. This may be a life or death situation, and safety overrides confidentiality.

Treatment Recommendations

If a patient is actively suicidal with thoughts of suicide and a plan to commit it and suicidal intent is stated or believed to be present, the clinician should take immediate action. Specifically, the patient should not be left alone. A one-to-one sitter can be ordered to monitor the patient's behavior. If a psychiatric consultation team is available, it may be called in to assess the status of a potentially suicidal patient as well as a patient suspected of having a depressive episode. If psychiatric consultation is not available, an actively suicidal patient may need to be transferred to a psychiatric facility for further management. Safety is the top priority, and the patient should be accompanied at all times. Medication intervention is recommended for suicidally depressed patients as well as patients experiencing major depressive episodes. Many effective antidepressants are available, but patients generally do not even begin to notice a change in mood for 2 weeks, with the full effect of antidepressants not present for months. A complete psychiatric evaluation is helpful in ruling out other possible diagnoses, as not everyone with suicidal thoughts is depressed.

Although the diagnosis of cancer increases the risk of depression and suicidality, some patients are very resilient. Many people speak of how they have reordered their lives with new priorities and even how their illnesses brought about positive changes. Periods of depression and difficulty coping with and adjusting to cancer before proceeding to live life as fully as possible are not unusual. Recognizing and intervening when a patient is suicidal can facilitate this.

Key Practice Points

- Agitation in the cancer patient may result from delirium, substance intoxication or withdrawal, medication side effects, or primary psychiatric disorders.
- Delirium is caused by underlying medical conditions or side effects of therapies, and treatment of it requires correction of these factors.
- Management of delirium consists of both pharmacologic and nonpharmacologic approaches.
- Cancer patients may experience agitation owing to prescribed medications such as antiemetics and corticosteroids.
- Patients with substance intoxication and withdrawal may present with agitation, and cancer patients should be routinely screened for substance abuse.
- Patients with cancer are at risk for exacerbation of psychiatric disorders, including depression, anxiety, mania, and psychosis.

- Suicide is a serious health concern, especially in patients with mental illness and cancer, who commit suicide at a rate approximately twice that in the general population.
- Any suicidal statements should be taken seriously, and the risk of suicide should be evaluated.
- If a patient presents with multiple symptoms of depression, assessing for any suicidal thinking is reasonable, because depression is the most common cause of suicidal thoughts.
- The degrees of suicidal risk differ, including active or passive suicidal thoughts, presence of a suicide plan, and suicidal intent. Different levels of risk require different levels of appropriate treatment to maintain patient safety.

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Chapter 14
Pediatrics

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Chapter Overview

Evaluation of an ill child with cancer in an emergency center can be daunting, even more so for a child with a previously undiagnosed condition or who is critically ill. This chapter outlines the basic tenets of care for acutely ill children with malignancies.

Introduction

Children with underlying malignancies can present to emergency centers (ECs) with a wide range of symptoms. These symptoms can arise from a previously undiagnosed cancer or represent a complication of disease progression or treatment. Management principles for such situations are consistent with emergency treatment guidelines published by the American Heart Association, American Academy of Pediatrics, and American College of Emergency Physicians.

These guidelines apply to all children regardless of etiology or circumstances and are based on careful initial and serial assessment of their vital functions and responses to interventions. When caring for a child with cancer *in extremis*, providing respiratory and hemodynamic support is more important than making the definitive diagnosis. Diagnosis and subsequent treatment must be carried out in partnership with a medical team familiar with pediatric cancer, preferably in a tertiary referral hospital. On-site pediatric oncologists and critical care specialists should be alerted at the time of admission of a child with cancer to the EC. Prompt referral and transfer should be initiated if the services of a pediatric oncology team are not available to the practitioner.

In the United States, the most common pediatric malignancies are leukemia (26 %), central nervous system tumors (17.5 %), and lymphoma (14.5 %). In general, the signs and symptoms of cancer in pediatric patients are nonspecific (e.g., malaise, fatigue, vomiting, weight loss, behavioral changes) and are commonly confused with those of other diseases.

Age Considerations

The age at which a child presents with cancer to an EC affects subsequent management and treatment of the cancer. Interestingly, researchers have suggested that the time from presentation to diagnosis is longer in older pediatric patients than in neonates. This may be a result of the increased testing that accompanies a neonatal sepsis workup. A high index of suspicion of cancer remains the key to diagnosing a malignancy regardless of the child's age.

Neonates and Young Children

Malignancies may occur in very young infants. These babies commonly present with poor feeding, failure to thrive, and irritability. Abnormalities in general appearance and vital signs, respiratory noise, and distress may be observed. Noisy breathing, drooling, and other physical examination findings may indicate masses in the extrathoracic or intrathoracic respiratory tract. Abdominal masses such as neuroblastomas, hepatoblastomas, and Wilms tumors may cause respiratory embarrassment or distress. Tachycardia or poor perfusion with hemorrhaging into masses may be noted in patients at any age. Leukemia and, less often, neuroblastoma may be manifested by pallor and bruising, occasionally leading to confusion about the cause of these symptoms with child abuse.

Malignancies in Older Children

The signs and symptoms of malignant disease at presentation vary in toddlers and school-aged children. Some children may have vague, poorly localized complaints and previously undergone evaluations. Leukemia frequently masquerades as an acute febrile illness, eluding prompt diagnosis. Persistent fever, progressive malaise, extensive bruising, and gingival swelling and/or hemorrhaging in the context of pancytopenia or significant leukocytosis may lead to the diagnosis of cancer in the EC (Fig. 14.1). Bone pain with refusal to walk may be noted in some cases. Marked hyperleukocytosis, defined as a white blood cell count greater than $100{,}000 \times 10^3$/mL, may be manifested by severe malaise, disturbances in the level of consciousness, and occasionally, respiratory distress.

The most common sign of brain tumors at presentation is headache. Classic tumor-related headaches last for several days to weeks, may cause sleep disturbances, are accompanied by nausea and vomiting, and increase in severity with straining or coughing. Headaches may be poorly localized, although some children with posterior fossa tumors may describe having headaches at occipital locations. Developmental delay or regression may occur in infants and toddlers. School-aged children may experience changes in their academic performance. Cranial nerve dysfunction and balance problems may be noted in children with brainstem or posterior fossa tumors. Seizures and decreased levels of consciousness may be presenting complaints, as well. Nonspecific symptoms such as poor appetite, subtle behavior changes, and nonlocalizing pain may be vague and persist for some time, usually a few weeks, occasionally prompting evaluation for gastrointestinal problems.

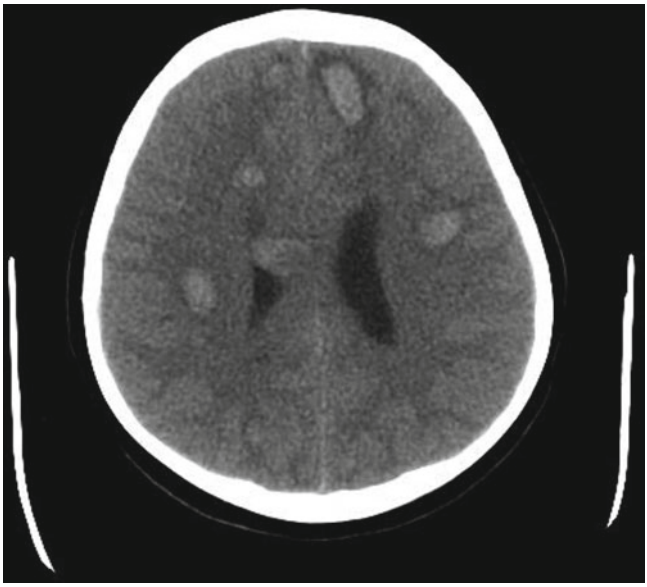

Fig. 14.1 Computed tomography scan of a 13-year-old patient presenting with persistent malaise, fever, and weakness. Decreased sensorium developed in the child while awaiting evaluation in an EC. His white blood cell count exceeded 400,000/mL. The scan revealed multifocal cerebral hemorrhages with associated edema leading to clinical brain death several days later

Management Principles

Shock may be evident in a pediatric patient upon admission to the EC. More often, however, early hemodynamic dysfunction and compensated shock are missed because children tend to have high resting heart rates and systemic vascular resistance and thus may have normal or even high blood pressure in the presence of hypovolemia and shock. Narrow pulse pressure (the difference between systolic and diastolic blood pressure) suggests hypovolemia or other causes of reduced stroke volume, whereas low diastolic pressure suggests inappropriately low systemic vascular resistance, most commonly because of sepsis. Hypovolemia manifested by tachycardia, tachypnea, narrow pulse pressure, cool extremities, and decreased mentation and urine output may be caused by dehydration resulting from intestinal loss, diabetes insipidus, or overt or occult hemorrhage.

Children with cardiogenic shock caused by sepsis or acquired cardiomyopathy usually have tachypnea with rales and may have jugular venous engorgement, a third heart sound, or hepatomegaly. Children with distributive shock caused by sepsis or, less often, anaphylaxis have tachycardia with a flushed appearance, low diastolic blood pressure, and evidence of end-organ dysfunction. Obstructive shock may result from tumors impinging on mediastinal vascular structures. These patients may

experience cardiac arrest with absolute or relative hypovolemia, underscoring the need to provide them with adequate fluid resuscitation with isotonic crystalloids, colloids, or indicated blood products and avoid indiscriminate use of sedative agents.

Seizures

Children with obvious or suspected seizure activity at presentation should be presumed to have status epilepticus. High-flow oxygen, assessment of airway patency, and vascular access are priorities for these patients. Hypoglycemia should be excluded by performing a bedside test within the first few minutes of presentation. Seizures may be controlled with the use of benzodiazepines and first-line antiepileptic drugs such as fosphenytoin, levetiracetam, and valproic acid. Phenobarbital must be used with extreme caution as it commonly causes respiratory depression.

Decreased Level of Consciousness

Children with decreased levels of consciousness should be presumed to have increased intracranial pressure until proven otherwise. Ensuring that their ventilation and hemodynamics are adequate is essential for maintaining adequate cerebral perfusion. Hypovolemia and hypotension should be immediately corrected. Unstable patients or those with declining vital signs are at imminent risk for cardiopulmonary arrest, and Pediatric Advanced Life Support protocols should be activated.

Originally developed for assessment of traumatic brain injury, the Pediatric Glasgow Coma Scale has proven to be reliable in assessing mental status in the general pediatric population (Table 14.1). Patients with declining Pediatric Glasgow Coma Scale scores should undergo intubation prior to computed tomography or other diagnostic testing. A score at or near 8 indicates the need to secure the airway after administration of lidocaine and analgesics and sedation. Three percent hypertonic saline may be superior to mannitol in that it aids maintenance of intravascular space while helping to correct increased intracranial pressure, particularly in the presence of hyponatremia. Dexamethasone should be administered to any patient with features suggestive of a space-occupying intracranial mass. Urgent neurosurgical consultation is mandatory for possible cerebrospinal fluid diversion or shunting.

Spinal Cord Compression

Spinal cord compression may complicate a variety of malignancies but occurs most often in children with solid tumors such as osteosarcoma and Ewing sarcoma. Any complaints of backache, especially when accompanied by weakness or neurologic

Table 14.1 Pediatric Glasgow Coma Scale

Eye opening	
Spontaneous	4
Speech	3
Pain	2
None	1
Verbal response	
Coos, babbles	5
Irritable cries	4
Cries to pain	3
Moans to pain	2
None	1
Motor response	
Normal spontaneous movement	6
Withdrawn to touch	5
Withdrawn to pain	4
Abnormal flexion	3
Abnormal extension	2
None	1

deficits, should be managed expeditiously with neurosurgical consultation, magnetic resonance imaging, and administration of high-dose steroids. Analgesia may be safely provided with carefully titrated doses of opioids. Hypotension or hypovolemia must be avoided to minimize the possibility of secondary spinal cord injury. Any delays in definitive therapy for spinal cord compression may result in permanent deficits.

Respiratory Distress

Any child who presents with respiratory distress is at risk for rapid progression to respiratory failure. Tachypnea may accompany sepsis, hypovolemia, and severe anemia and may be easily missed given the increased resting respiratory rate common in children. Refusal of a patient to adopt a supine position may indicate the presence of a mediastinal mass impinging the airway and must always be managed with great caution, avoiding sedation and positioning that may precipitate respiratory arrest. Stridor may respond to the use of nebulized racemic epinephrine while the patient is awaiting otolaryngologic consultation. Children with small airway disease, marked by expiratory wheezing, may benefit from nebulization with levalbuterol. Children with known or suspected myocardial dysfunction may present with pulmonary edema, which may be mitigated by administration of loop diuretics at carefully titrated doses.

All patients who present with these features merit very close observation, as subtle abnormalities can quickly culminate in overt respiratory failure and life-threatening tissue hypoxia. Children, particularly small infants, tolerate these challenges poorly

because of their small collapsible airways; compliant thoraces with immature, easily fatigued muscles; and limited functional residual capacity. A significant fraction of cardiac output may be diverted when breathing effort is increased, underscoring the importance of timely ventilator support in critically ill children.

Acute lung injury may be indicated by progressive increases in work of breathing with hypoxemia unresponsive to delivery of supplemental oxygen via a simple face mask at presentation. Children with respiratory distress should be admitted to the intensive care unit (ICU) for consideration of assisted ventilation.

Intubation for respiratory failure of any etiology is greatly facilitated by proper preparation. Acutely ill children commonly have delayed gastric emptying. Therefore, they should be considered to have full stomachs and intubated using appropriate precautions. Cuffed endotracheal tubes are preferred for all children to maintain mean airway pressure and recruit small airways. In the absence of overt pulmonary edema and cardiac failure, most children benefit from receiving a crystalloid or colloid bolus to ensure optimal intravascular volume. Correction of thrombocytopenia and coagulopathy is desirable prior to intubation to minimize bleeding, which may obscure the airway.

Treatment with atropine minimizes airway secretions while preventing potentially devastating vagally mediated bradycardia and thus should be considered for all patients, particularly young infants. Ketamine is a valuable agent because of its profound analgesic and amnestic effects as it does not cause the hemodynamic instability that opioids (particularly morphine), propofol, and benzodiazepines can promote. The use of etomidate in a hemodynamically unstable child is discouraged except when increased intracranial pressure is strongly suspected, as it may cause adrenal insufficiency and has been associated with increased mortality rates in some studies.

Optimal tidal volumes generally range from 6 to 8 mL/kg ideal body weight, with inspiration times and frequencies titrated to ensure adequate ventilation while minimizing dynamic hyperinflation. High peak airway pressures and low end-expiratory pressures should be avoided during arrangement of a transfer of a patient to an ICU. Adequate analgesia, sedation, and neuromuscular blockade must be used as indicated to prevent displacement of the endotracheal tube.

Febrile Neutropenia and Sepsis

Febrile neutropenia is perhaps the most common complication of chemotherapy. Although the majority of children who have it can be integrated into comprehensive general care unit-based protocols targeting the most common gram-positive and -negative pathogens (including viridans streptococci, *Escherichia coli*, and *Pseudomonas aeruginosa*), some children present with evidence of a systemic inflammatory response and compensated shock, with tachycardia, vasomotor tone abnormalities, and impaired perfusion, which is manifested as subtle changes in behavior or consciousness level or decreased urine output before progression to septic shock.

Prompt, accurate assessment of a child's hemodynamics with indicated resuscitative measures, including timely (within the first few minutes after presentation) administration of appropriate antimicrobials having broad-spectrum coverage such as cefepime and vancomycin, is essential for a successful outcome. Children differ from adults in that they typically need large amounts of isotonic crystalloid to repair relative and absolute hypovolemia, tend to present with or experience hypoglycemia and hypocalcemia, have a propensity for development of respiratory failure, and experience late preterminal development of hypotension. Delays in the recognition and appropriate management of the shock state cause proportional increases in morbidity and mortality rates in children. Conversely, optimal management in accordance with published guidelines improves clinical outcomes as assessed in a variety of hospital settings.

The most recent update of the American College of Critical Care Medicine's clinical guidelines for the management of septic shock in neonatal and pediatric patients highlights the importance of a comprehensive, systematic, time-sensitive approach. Under these guidelines, the patient's airway, breathing, and circulation are managed upon presentation with administration of high-flow supplemental oxygen in all cases. Vascular access is obtained using peripheral intravenous or intraosseous needles until a qualified clinician performs central venous line placement. Response to aggressive fluid resuscitation with the use of an isotonic crystalloid or colloid in amounts frequently well in excess of 60 mL/kg is monitored clinically with the goal of restoring the heart rate, capillary refill, and blood pressure to normal threshold values within the first hour after presentation. Inotropic infusions, especially of dopamine (at least 10 μg/kg/min) and low-dose epinephrine (0.05–0.30 μg/kg/min), are initiated if necessary via peripheral access until central venous cannulation is accomplished. The airway is secured via intubation with preferential use of atropine and ketamine to minimize the hemodynamic repercussions of the procedure. Patients at relative or absolute risk for adrenal insufficiency must promptly receive supplementation with hydrocortisone within the first hour of care. Infusion of packed red blood cells or other blood products may be required. Fresh frozen plasma should be infused slowly when indicated.

Serial physical examination provides clues about underlying vascular resistance and has led to the creation of the commonly used terms "warm shock," which is associated with high cardiac output and improved outcomes, and "cold shock," which is usually associated with significant organ dysfunction, high systemic vascular resistance, and depressed cardiac output. Clinical observations can be supplemented by serial assessments of central venous saturation in samples of blood drawn via intravenous lines in the superior vena cava.

Infusions of vasoactive agents can be titrated to improve cardiovascular performance. Specifically, α-adrenergic medications such as norepinephrine and vasopressin are preferred for hypotensive patients with warm shock, whereas inovasodilators such as milrinone and nitrovasodilators are preferred for normotensive patients with cold shock. Epinephrine (with subsequent addition of norepinephrine if required) is preferred as the primary agent for cold shock with hypotension.

Persistent cathecolamine-resistant shock requires consideration of adrenal insufficiency with a low threshold for administration of hydrocortisone and of potentially correctable problems such as pneumothorax, pericardial effusion, and abdominal hypertension. Whereas blood and urine cultures are necessary for a diagnosis of sepsis, administration of antibiotics never should be delayed because of difficulty in obtaining culture specimens. Lumbar puncture should be avoided in the EC as it carries serious risks such as cardiac arrest and does not enhance urgent management.

Meticulous attention must be paid to all aspects of a child's care. Analgesia, sedation, and neuromuscular blockade should be performed carefully to minimize hemodynamic problems. Ongoing fluid resuscitation must continue while preventing hypervolemia, which may compromise organ function. Lung-protective strategies and prevention of hypoglycemia and hyperglycemia decrease the incidence of secondary end-organ injury in vulnerable populations. Co-existing endocrine dysfunction, including adrenal insufficiency and thyroid dysfunction, should be carefully considered for all patients. Possible sources of infection, including pre-existing vascular lines, should be taken into account.

New Diagnosis of Leukemia

Hyperleukocytosis, defined as a white blood cell count greater than $100{,}000 \times 10^3$/mL, may result in rapidly evolving organ dysfunction, including intracranial hemorrhage and cerebral edema. This oncologic emergency must be treated aggressively with the assistance of a pediatric hematologist/oncologist. Initial interventions should include indicated resuscitative measures, hydration, treatment with rasburicase, and administration of blood products in the presence of bleeding. Hyperleukocytosis may progress very rapidly. The white blood cell count may double in hours, mandating frequent blood counts until the patient's condition has stabilized. Initiation of leukapheresis or exchange transfusion may be difficult to arrange, particularly in small children, and therefore must be considered early in the course of a child's leukemia.

Hydration begins with rapid administration of 20-mL/kg boluses of an isotonic crystalloid such as normal saline or Ringer lactate solution; 5 % albumin may be considered, as well. Once intravascular volume is restored in a child with a new diagnosis of leukemia, the usual fluid prescription is given at a dosage of 3000 mL/m^2 per day, usually with isotonic dextrose-containing crystalloids. Bicarbonate or acetate-containing solutions are used by some clinicians. Electrolyte, calcium, and phosphorus levels must be monitored closely given the risk of spontaneous or drug-induced tumor lysis syndrome. Treatment with allopurinol or rasburicase may be started in the EC to minimize the incidence of uric acid nephropathy under the direction of an experienced clinician. Spurious hypokalemia and hyperkalemia may be observed and can be minimized by appropriate sample handling. True electrolyte abnormalities must be managed appropriately. Hypocalcemia is common and should be treated cautiously if symptomatic.

Broad-spectrum coverage with antibiotics such as cefepime and vancomycin should be administered if there is any suspicion of infection. Meropenem can be given if a patient has a confirmed history of allergy to cephalosporins. Linezolid and daptomycin are considerations for patients with true vancomycin allergies. Subspecialty infectious disease consultation is recommended in such cases.

Severe anemia may be managed via transfusion of packed red blood cells with additional precautions taken for children with hyperleukocytosis given their risk of exacerbating leukostasis or with long-standing anemia given their risk of precipitating congestive heart failure. Severe thrombocytopenia, usually defined as a platelet count less than 30,000/μL, should be treated with platelet transfusion to minimize intracranial hemorrhage. Isolated thrombocytopenia may develop in children with nonmalignant conditions such as idiopathic thrombocytopenic purpura. Hematologic consultation is required for diagnosis and optimal management in such situations.

The Acutely Bleeding Child

Acute bleeding may complicate many childhood malignancies. In particular, intracranial hemorrhage is heralded by headache, nausea, vomiting, and alterations in consciousness level. The airway must be secured prior to any transport or imaging of patients whose condition is rapidly deteriorating. Acute, sometimes catastrophic airway hemorrhage may occur in children with malignancies that erode vascular structures. Subspecialty consultation is necessary to isolate and control the source of bleeding. Diffuse alveolar hemorrhage may be marked by respiratory distress; frothy, bloody sputum; and rapidly progressive hypoxemia and is managed using positive pressure ventilation and treatment with factor VII and steroids. Significant bleeding into the abdomen or retroperitoneum may occur in a relatively occult fashion. Children with such bleeding eventually experience abdominal pain, distention, profound anemia, and hypovolemic shock.

Blood Products

Blood products, including packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitates, all have specific indications for transfusion. Packed red blood cells are administered cautiously in patients with hyperleukocytosis because of the risk of increasing blood viscosity. Patients with long-standing anemia usually tolerate gradual packed red blood cell transfusion. Patients with severe, acute anemia and features of shock need more rapid transfusion. Transfusion of platelets does not exacerbate the increase in blood viscosity that occurs in patients with hyperleukocytosis and should be considered for all severely thrombocytopenic patients, particularly infants and patients at risk for intracranial hemorrhage. Transfusion of fresh frozen plasma is very useful for coagulopathic patients; however, it should

Table 14.2 Blood product replacement guidelines

Blood product	Dose	Comments
Packed red blood cells	10–15 mL/kg	
Fresh frozen plasma	10–15 mL/kg	Must be infused slowly
Platelets	1 U/10 kg	
Cryoprecipitate	2 U/10 kg	
Factor VII	100 μg/kg	"Round off" to 1.2-, 2.4-, or 4.8-mg vial to limit cost

never be given as a bolus. Severe hypofibrinogenemia is corrected by transfusion of cryoprecipitates. Factor VII is very useful, although it is ineffective if severe hypofibrinogenemia is present. Repeat dosing may be necessary in the EC because of the relatively short factor VII half-life of 2 h (Table 14.2).

Electrolyte Issues

Disorders in water, sodium, and calcium balance are common in acutely ill children. A careful examination of the child's medical history, estimation of the child's input and output over the preceding day, and measurement of the child's serum and urinary sodium levels and osmolality may help identify the cause of hyponatremia. This is important, because the most common intervention for management of inappropriate antidiuretic hormone secretion is fluid restriction, whereas cerebral salt wasting must be treated with sodium and water repletion. Hypernatremia is most common in children with underlying diabetes insipidus and is best managed with administration of 0.9 % saline until normalization of hemodynamics followed by restoration of the estimated water deficit over a longer period of time using an individualized intravenous fluid prescription.

Hypocalcemia is common in acutely ill children and should be treated with calcium infusions as indicated. Calcium chloride is generally preferred in emergencies, including hyperkalemia; however, rapid infusion of it may result in bradycardia. Hypercalcemia is relatively uncommon in pediatric patients. Management of hypercalcemia includes rehydration, treatment with furosemide, and, in some cases, treatment with agents such as steroids, calcitonin, and bisphosphonates.

Analgesia and Sedation

Analgesia and sedation must be induced judiciously, particularly for children with hemodynamic instability, with the use of short-acting agents with minimal hemodynamic repercussions (Table 14.3). Analgesics are not effective sedatives, and sedatives have no analgesic properties. Emergency procedures can be safely performed in most patients, with the possible exception of those having increased intracranial

Table 14.3 Emergency drugs in pediatric emergency medicine

Drug	Intravenous dose	Comments
Fentanyl	1–2 μg/kg	Infuse slowly
Midazolam	0.025–0.050 mg/kg	Titrate gradually 1–2 mg at a time
Ketamine	1–2 mg/kg	Drug of choice for intubation
Rocuronium	1 mg/kg	Ensure adequate ventilation
Fosphenytoin	20 mg/kg	
Levetiracetam	20 mg/kg	
Cefepime	50 mg/kg	Up to 2 g
Vancomycin	15 mg/kg	Up to 1 g
Acetaminophen	15 mg/kg	

pressure, using administration of atropine and ketamine followed by small titrated doses of benzodiazepines to minimize emergence phenomena.

Treatment with fentanyl has distinct advantages over that with morphine in patients with hypotension or bronchospasm in that the former is much less likely to cause histamine release. However, fentanyl may cause chest-wall rigidity when rapidly infused in large doses, particularly in small infants. Fentanyl is usually given to critically ill patients as a continuous infusion titrated to analgesia, which is sometimes difficult to judge when a patient is also receiving sedatives or undergoing neuromuscular blockade.

Similarly, short-acting agents are given in continuous infusions in the initial phases of stabilization to induce sedation. The most commonly used sedative agent in pediatrics is midazolam. Treatment with propofol to induce sedation should be limited to carefully selected patients and performed by experienced clinicians, as marked drops in systemic vascular resistance and myocardial performance may precipitate cardiac arrest in vulnerable patients.

Treatment with a local anesthetic is an important adjunct to procedures such as intravascular line placement. Also, children with chronic pain benefit from prompt contact with their managing services so that they can begin receiving effective multimodal therapy in the EC.

The Child with Diagnosed Cancer

Because children with cancer frequently receive treatment at tertiary referral centers, they may present to community ECs with a variety of complaints, from the mundane (central line occlusion) to the life-threatening (sepsis). Fortunately, these children are often accompanied by their caregivers, who have contact information for the treating team in the event of urgent telephone consultations. Parents with sick children should be encouraged to report to the nearest EC (and to use emergency medical services) when in doubt and avoid long drives to cancer centers. Examination of the patient's airway, breathing, and circulation remain paramount regardless of the underlying

diagnosis. Careful continuous monitoring using pulse oximetry, frequent assessment of vital signs, and observation by experienced clinicians is crucial. Bedside assessment of blood glucose levels should be performed upon admission and is particularly important for young infants and critically ill children. Point-of-care evaluation of blood gases, electrolytes, and hematocrit may help guide immediate management of unstable children. All laboratory work, including complete blood counts, chemistry panels, coagulation profiling, and blood typing and screening, should be performed in an expedited manner upon admission to the EC. Additionally, blood cultures, urinalysis with culture, and a chest radiograph should be performed. Treatment with antibiotics never should be delayed even if securing appropriate cultures is difficult (Table 14.3). Specialized imaging or testing may be indicated. Preparation for transfer to a pediatric ICU should be initiated as soon as a critical illness is recognized.

Key Practice Points

- The mainstay of emergency treatment for children with cancer is preservation of respiratory and hemodynamic function regardless of the etiology.
- Broad-spectrum antibiotics should be administered as soon as possible if a child appears to be ill even in the absence of fever and whenever neutropenic fever is suspected. Earlier is better—any delay in antibiotic therapy may contribute to a poor outcome.
- Rapid transfer to a tertiary care center should be considered early in the process of evaluating a sick child with cancer.
- Suspicion of an undiagnosed malignancy must be maintained when evaluating nonspecific, persistent, worsening symptoms in children seen in the EC.
- Computed tomography is warranted in the evaluation of headaches accompanied by any localizing neurologic signs in the EC or if a new or a significant change in seizure pattern occurs.
- Continuous observation of the patient by skilled nursing and medical personnel until transfer to a pediatric ICU is absolutely essential.

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Suggested Readings

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Chapter 15
Obstetric and Gynecologic Emergencies in Cancer Patients

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Chapter Overview

Gynecologic emergencies in cancer patients can be significant, and knowledge of the approach to treatment of these emergencies is crucial to optimizing the patient's oncologic and gynecologic care. This chapter outlines the basic principles of diagnosis and treatment of obstetric and gynecologic emergencies in cancer patients.

Introduction

With more than 700,000 women estimated to receive a cancer diagnosis in 2009, gynecologic emergencies are becoming increasingly common in patients with cancer. In all cases, evaluation of the patient requires a thorough medical history and pelvic examination. Determination of pregnancy status is crucial, as the algorithm for assessment of pregnant patients differs significantly from that for nonpregnant patients. Rapid evaluation of patients and distinguishing between surgical and medical gynecologic conditions is key. Hemorrhage and hemodynamic instability are common sequelae of many gynecologic disorders and may be life-threatening if not identified and treated early. A basic understanding of gynecologic infections, surgical emergencies, and comorbidities commonly associated with cancer treatment is necessary, as is an appreciation of the potential effects of therapeutic interventions on a developing fetus. Consultation with an obstetrician/gynecologist should be considered when surgical intervention is required, the patient is pregnant, or the diagnosis is in doubt.

Pregnancy in the Cancer Patient

A diagnosis of cancer is often overwhelming, especially for pregnant patients. Medical decision making for such patients can be extremely complex, as both the health of the mother and the safety of the fetus must be considered. Appropriate treatment planning is influenced by the indications for treatment as well as the patient's feelings regarding continuation of the pregnancy once she has been properly counseled regarding the risks and benefits of therapy.

Because cancer is the second leading cause of death in reproductive-age women, the fact that cancer can develop in pregnant individuals is not surprising. An estimated 0.1 % of pregnancies are complicated by concomitant cancer diagnoses, accounting for nearly 5000 cases in the United States annually. Pregnancy does not increase the risk of malignancy, and the incidence of specific malignancies in pregnant women is similar to that in nonpregnant women. With women increasingly delaying pregnancy, cancer rates in pregnant women are expected to increase. In addition, with improving multidisciplinary treatment modalities for cancer, a

number of women who survive childhood or juvenile cancers are able to become pregnant, thereby introducing management of pregnancy into the cancer surveillance schema.

The cancer diagnosed most often in pregnant women is cervical cancer, with an estimated incidence of 10–1000 cases per 100,000 pregnancies. Other malignancies frequently associated with pregnancy include breast cancer, malignant melanoma, Hodgkin and non-Hodgkin lymphoma, and ovarian cancer. Although the majority of deaths associated with cancer in pregnant patients result from treatment of malignancy, the disease itself may pose specific risks to the fetus. Metastasis to the placenta is very common in patients with malignant melanoma, accounting for more than one third of all metastases observed in products of conception. When melanoma metastasizes to the uterus, the fetus itself is affected in 22 % of cases, and a large proportion of affected fetuses will subsequently die of the disease. In addition, women with Hodgkin lymphoma have a risk of stillbirth greater than the baseline population risk, and physicians have observed markedly lower fetal birthweights for patients with breast cancer than for individuals without it.

Chemotherapy and Pregnancy

All chemotherapeutic regimens are potentially teratogenic and mutagenic, and administration of chemotherapy to a pregnant woman is complicated by concerns about fetal growth restriction, mental retardation in offspring, and the potential for future malignancies. Investigators have performed controlled studies of chemotherapy in pregnant laboratory animals, but extrapolation of the results of such studies to humans must be done with caution. Because no large prospective studies have evaluated the effects of chemotherapy during pregnancy, treatment regimens for pregnant patients with cancer are frequently selected based on the results of case reports and small retrospective studies. An important point to remember is that each patient is unique, and the balance between maximizing maternal outcome and minimizing fetal toxicity depends heavily on consideration of comorbidities, fetal gestational age at diagnosis, and treatment goals.

Pregnancy is a significant physiologic departure from the nonpregnant state. Pregnant women have an increase in circulating blood volume of 50 %, reduced gastrointestinal motility, and an increased glomerular filtration rate. Thus, the absorption, metabolism, and excretion of chemotherapeutic agents in pregnant patients may differ from that in nonpregnant ones. In addition, hypoalbuminemia associated with pregnancy results in decreased plasma protein for drug binding, which may increase medication bioavailability. Keeping in mind that most drugs cross the placenta, taken together, these factors may contribute to a hostile uterine environment for the fetus when cytotoxic medications are administered.

The developmental stages for embryos and fetuses are well defined. These stages are separated into the preimplantation (fertilization to implantation), embryonic

(gestational weeks 2–8), and fetal (week 9 to term) periods. Physiologic principles specific to these stages explain the effects of chemotherapy on the fetus.

In the first several days after fertilization, cleavage of the zygote proceeds through the 12-cell morula stage to formation of the blastocyst with an early embryonic pole. Implantation of the blastocyst to the wall of the uterus occurs about 6–7 days after fertilization. The blastocyst is relatively resistant to the effects of teratogens because it has yet to be connected with the maternal circulation. However, once this connection is established, a blastocyst exposed to cytotoxic drugs may be severely damaged and/or spontaneously abort.

The period of gestation when the developing fetus is most susceptible to the effects of teratogens is the first trimester. By the end of the fourth week, the primitive heart begins partitioning, and the neural tube closes. The limbs, facial features, and ears develop by the end of the sixth week. Because the number of progenitor cells is small and they organize and differentiate rapidly, an insult at this point in development can be catastrophic. Fetal malformation rates are reported to be as high as 50 % when chemotherapy is given during this time. For this reason, physicians generally recommend delaying chemotherapy until the second trimester.

Organogenesis is complete by the 12th week of gestation, but cortical pathway development and pulmonary and gonadal differentiation continue. Although the majority of reported studies of infants exposed to chemotherapy in utero did not include indefinite observation of the subjects, because of the continued neurologic development in the second and third trimesters, delayed development is a theoretical consequence of fetal chemotherapy exposure, as are fertility issues when the affected fetus reaches sexual maturity.

Fetal metabolism of drugs is limited. The hepatic cytochrome P450 isoforms that metabolize chemotherapeutic drugs are not mature until several weeks into the neonatal period, so chemotherapy should be delayed for 3 weeks prior to delivery to prevent toxic effects in the newborn child. The chemotherapy method and timing of delivery in the pregnant patient are equally important, as a myelosuppressed fetus may be at risk for both sepsis and intracranial hemorrhage. The patient and her obstetrician should discuss the use of a cesarean section.

In the postpartum period, patients should consider cessation of breast feeding during chemotherapy. Drugs such as cyclophosphamide, doxorubicin, and methotrexate are secreted into breast milk and may cause immunosuppression, neutropenia, and poor growth in infants exposed to them.

Effects of Specific Chemotherapeutic Agents

Taxanes

Taxanes are microtubule inhibitors frequently used in the treatment of ductal carcinoma of the breast and epithelial ovarian cancer. When given prenatally in rat models, taxanes do not seem to affect either organogenesis or subsequent cognitive

ability. However, when given perinatally or during the neonatal period, they have caused significant physiologic delays in development. In case reports, authors have noted no observed negative effects of taxanes on human organ development when given in the second and third trimesters, although low birth weights may be seen.

Platinum Agents

In the majority of cases, platinum agents are given during pregnancy for the treatment of gynecologic malignancies, specifically, cervical and ovarian cancers. Platinum readily crosses the placenta, and researchers have found it in umbilical cord blood specimens. Administration of platinum agents in the second and third trimesters is associated with hydramnios, intrauterine growth restriction, neonatal myelosuppression, and transient renal insufficiency. However, in a review of 43 pregnant patients with a variety of gynecologic and nongynecologic cancers treated with platinum agents, adverse effects occurred in less than 25 % of fetuses and neonates.

Antimetabolites

The majority of birth defects in offspring of cancer patients are related to administration of the folate antagonists methotrexate and aminopterin during the first trimester. Methotrexate is commonly used to induce abortion and treat ectopic pregnancies. When given in the first trimester, methotrexate induces significant craniofacial and skeletal abnormalities, joint contractures, and growth retardation in offspring. Case reports have even demonstrated associations between methotrexate administration and structural brain malformations, including holoprosencephaly. Children with mothers given aminopterin early in pregnancy at are risk for aminopterin syndrome, which is characterized by cranial dysostosis, external ear anomalies, hypertelorism, micrognathia, and cleft palate. In addition, treatment with the pyrimidine antagonist 5-fluorouracil has been associated with increased apoptotic and reduced mitotic rates in the telencephalons of fetal rats, and authors have reported multiple congenital anomalies in newborn children exposed to 5-fluorouracil in the first trimester.

Antibiotics

The anthracycline antibiotics doxorubicin and daunorubicin are frequently used to treat breast cancer and leukemia. Large reviews have demonstrated the safety of these two drugs. In a 2004 review of 160 pregnant patients given anthracyclines, the fetal outcome was normal in 73 % of the cases. However, fetal death, prematurity, and malformations occurred in 9 %, 6 %, and 3 % of the cases, respectively. Patients receiving treatment during the first trimester and/or more than 70 mg/m^2

doxorubicin per cycle had an increased risk of adverse events. The authors concluded that the overall fetal risk is small when low doses of anthracyclines are administered and treatment is delayed until the second trimester.

Authors have reported no adverse fetal effects with the administration of bleomycin, although it is rarely used alone, as it is given more often in combination with other chemotherapeutic agents. Bleomycin is known to cause pulmonary toxic effects, which may be exacerbated by administration of oxygen to the mother during labor and delivery. Thus, pregnant patients needing general anesthesia who have been exposed to bleomycin should be given oxygen at room-air concentrations.

Vinca Alkaloids

Investigators have shown that vincristine and vinblastine induce neurologic abnormalities associated with defects in myelination in laboratory animals. However, case reports on the use of vinca alkaloids in humans have not demonstrated any associated neonatal malformations with up to 2 years of follow-up.

Etoposide

As with bleomycin, data on single-agent administration of etoposide in pregnant patients are scarce. However, authors have reported association of neonatal pancytopenia with the use of regimens that include this drug during the second trimester.

Targeted Agents

With increasing use of molecular and biologic therapies for cancer, the opportunities for fetal exposure to these agents are also increasing. The majority of reported case reports on treatment with targeted agents have focused on breast cancer patients with in utero exposure to trastuzumab and lapatinib, both of which are HER2/neu-targeted agents. Administration of these drugs is associated with a high risk (greater than 60 %) of oligohydramnios or anhydramnios, renal failure, and neonatal death. Therefore, use of these agents in pregnant patients should be restricted, if possible. Administration of rituximab, a monoclonal anti-CD20 antibody used in the treatment of non-Hodgkin lymphoma, has been associated with premature B-cell depletion and transient pulmonary insufficiency in neonates.

Radiation Therapy and the Pregnant Patient

As with chemotherapy, administration of radiation therapy during pregnancy requires careful consideration of therapeutic goals and balancing maternal and fetal outcomes. The greatest risk to the developing fetus is associated with radiation

exposure before 10 weeks of gestation. At fewer than 8 days of gestation and during the blastocyst stage, radiation exposure is invariably lethal to embryos. Radiation exposure during the remainder of embryogenesis is associated with fetal malformations, including a high incidence of microcephaly, growth retardation, sterility, and subsequent malignancy. Data on women undergoing curative irradiation during the embryonic period have demonstrated that use of a dose as low as 3.6 Gy is capable of inducing abortion. Because central nervous system development in the fetus continues beyond 10 weeks of gestation, the risk of microcephaly and severe mental retardation when the fetus is exposed to radiation is persistent. At doses greater than 0.5 Gy, researchers have observed substantial drops in the intelligence quotients of exposed offspring. In addition, radiation exposure has been associated with increases in the relative risk of malignancy of more than 50 % in the offspring of exposed women. Many of these malignancies are hematogenous in origin.

A threshold dose below which radiation therapy is deemed to be safe in pregnant patients has yet to be identified, although some studies have demonstrated that fetal effects appear to be minimal at doses less than 0.01 Gy. A key consideration for many practitioners is the amount of radiation exposure associated with current imaging modalities. Of note is that no single diagnostic radiologic procedure results in radiation exposure to a degree that would threaten the viability of a fetus at any point in gestation. The estimated doses fetuses are exposed to with commonly used radiologic procedures are listed in Table 15.1.

Researchers have suggested the use of in utero exposure to more than 0.1 Gy of radiation as a threshold for consideration of elective termination of a pregnancy. However, case reports of administration of 0.5 Gy during the first trimester did not demonstrate a substantial risk of fetal malformation. Exposure to a single X-ray during pregnancy is not an indication for a therapeutic abortion. Irradiation of the abdomen and/or pelvis at doses used to treat cancer should be avoided, if possible. However, if such treatment is necessary, the radiation oncologist, the patient, and a

Table 15.1 Estimated fetal radiation doses with common diagnostic procedures

Procedure	Fetal dose (cGy)
Chest X-ray (2 views)	0.00002–0.00007
Abdominal film (single view)	0.1
Intravenous pyelography	≥1
Hip film (single view)	0.2
Mammography	0.007–0.020
Barium enema/small bowel series	2–4
CT scan of the head	<1
CT-based pulmonary angiography	<1
CT scan of the abdomen/lumbar spine	3.5
CT-based pelvimetry	0.25

Based on data from Bodurka DC, Burke T. Obstetric and gynecologic emergencies. In: Yeung S, Escalante C, eds. Oncologic Emergencies. Hamilton, Ontario, Canada: BC Decker; 2002:433–440

maternal fetal medicine specialist must have a frank, open discussion to assess the risk to both mother and child and decide upon a plan of action.

Vaginal Hemorrhage

Acute vaginal bleeding can be life-threatening. Without exception, all women of reproductive age experiencing such bleeding should undergo a urine pregnancy test, as the results significantly impact differential diagnosis of the cause of the bleeding (Fig. 15.1). Such patients should be hemodynamically stabilized, which includes establishing large-bore intravenous access, initiating aggressive fluid resuscitation, and repleting blood products. In cases of significant hemorrhage, transfusion of uncross-matched blood may be considered.

If the pregnancy test is positive, the differential diagnosis for vaginal bleeding during the first trimester includes complete, incomplete, or missed abortion; gestational trophoblastic neoplasia; and molar or ectopic pregnancy. Pelvic examination will help establish whether the cervical os is open or closed, whether products of conception are being expelled by the uterus, the size of the uterus, and whether any appreciable adnexal masses are present. Vaginal lesions that appear to be blue in color should not be subjected to biopsy analysis, as they may be metastatic choriocarcinomas; biopsy may result in uncontrollable hemorrhaging. Also important is determining the maternal blood type, as Rh-negative women should receive $Rh_o(D)$ immune globulin (RhoGAM) to prevent Rh isoimmunization and hydrops fetalis.

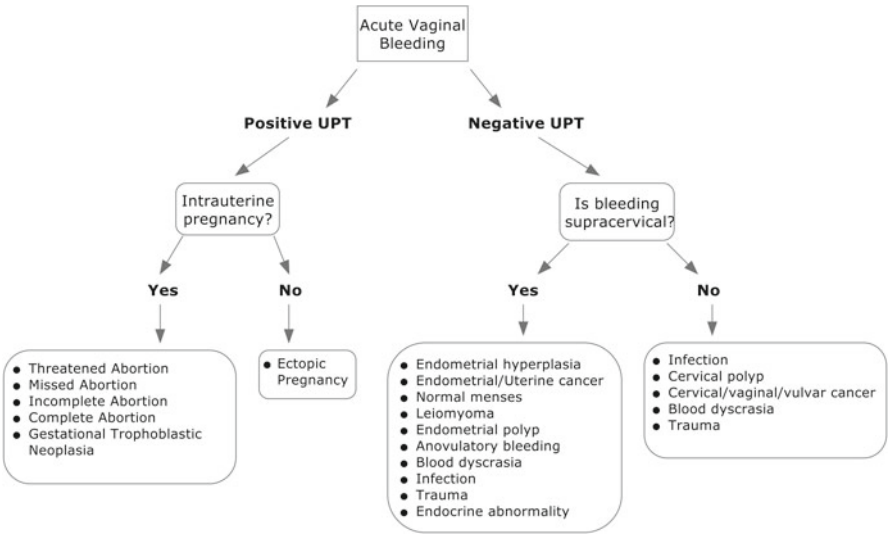

Fig. 15.1 Differential diagnosis of acute vaginal bleeding. *UPT* urine pregnancy test

Pregnant patients in the second or third trimester who present with vaginal bleeding should receive immediate care managed by an obstetrician. Diagnostic considerations include preterm and normal labor, premature membrane rupture, premature cervical dilatation, placenta previa, placental abruption, and vasa previa. These patients should not undergo vaginal examination until ultrasonographic confirmation of the location of the placenta to avoid inadvertent disruption of a placenta previa or low-lying placenta. They also should be promptly transferred to a labor and delivery unit capable of fetal monitoring and emergent cesarean section.

Women with gestational trophoblastic disease commonly present with vaginal bleeding and a positive pregnancy test. Risk factors for this disease include prior molar pregnancy and advanced maternal age. Upon physical examination, the cervix is usually closed, and the uterus is larger than expected for women at gestational age. Transvaginal ultrasonographic imaging reveals a pathognomonic "snowstorm" pattern of heterogeneous echoes. Rarely, fetal parts may be seen sonographically. Serum levels of β-human chorionic gonadotropin (hCG) in these patients are markedly elevated and may subsequently be used to assess response to surgical or medical management. Chest radiography is recommended to rule out the presence of pulmonary metastases. If nodules are seen on chest X-rays, imaging of the brain should be performed. Patients with gestational trophoblastic disease should be admitted to the hospital, with subsequent treatment plans developed in coordination with an obstetrician/gynecologist.

If the pregnancy test for a patient with vaginal hemorrhage is negative, a pelvic examination often suggests the diagnosis for her bleeding. Friable areas of the cervix should be subjected to biopsy analysis, and, if possible, cervical cytologic specimens should be obtained and examined. Cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* should be obtained using an endocervical swab. Significant hemorrhaging from the cervix may be treated with Monsel's solution or silver nitrate, both of which chemically cauterize areas of bleeding. In cases in which this treatment is unsuccessful, such as those of acute hemorrhaging from a cervical carcinoma, tight vaginal packing may be used. As a last resort, uterine artery embolization, emergent pelvic radiation therapy, and surgical bilateral hypogastric artery ligation may be performed. In addition, thorough vulvovaginal examination should be performed to rule out occult cutaneous malignancies.

If the cervix and vagina appear to be normal and the source of the bleeding is likely supracervical, an endometrial biopsy should be considered. This is especially important for women older than 35 years and those who are morbidly obese, as endometrial pathology is more common in these groups than in others. Transvaginal ultrasonography can identify areas of endometrial thickening and structural anomalies in the uterus, such as leiomyomas. When no anatomic abnormalities are present, the most common diagnosis is anovulatory bleeding; other endocrinologic pathologies (e.g., hypothyroidism) and hematologic dyscrasias (e.g., von Willebrand disease) should be excluded. When significant uterine hemorrhaging occurs, conjugated estrogen (Premarin) may be given intravenously at a dose of 25 mg every 4 h for 24 h or until the bleeding stops. Adequate prophylaxis for deep venous thrombosis should be initiated if intravenous estrogen is used given its prothrombotic activity.

Alternatives to estrogen administration in women with less acute hemorrhaging are tapered administration of combined estrogen/progestin oral contraceptive pills and progestin-based therapy alone.

Ectopic Pregnancy

Ectopic pregnancy is the leading cause of pregnancy-related deaths during the first trimester. Early diagnosis is important for maternal welfare because it allows for conservative nonsurgical treatment, thereby preventing potentially catastrophic hemorrhaging associated with a ruptured ectopic pregnancy. The incidence of ectopic pregnancy has increased markedly in the United States since 1970, going from 4.5 per 1000 pregnancies to 19.7 per 1000 pregnancies in 1992. However, the number of deaths caused by ectopic pregnancy has decreased 10-fold over the same period, in part owing to improved ultrasonographic detection of it and increasingly sensitive β-hCG assays.

The majority of ectopic pregnancies implant in a fallopian tube, although they may implant on the ovary, cervix, or uterine cornua or in the abdominal cavity. Investigators have identified a number of well-established risk factors for ectopic pregnancy, including prior tubal surgery, genital tract infections leading to pelvic inflammatory disease (PID), prior ectopic pregnancy, and in utero exposure to diethylstilbestrol. A single ectopic pregnancy increases the risk of a subsequent ectopic pregnancy more than 12-fold, whereas women with a history of either confirmed or suspected PID have a fourfold increased risk. Furthermore, epidemiologic studies have suggested that advanced maternal age, smoking, prior abortion (spontaneous or induced), prior abdominal surgery, multiple sexual partners, prior treatment of infertility, and use of an intrauterine device for contraception are associated with increased risk of ectopic pregnancy.

The classic triad of symptoms of an ectopic pregnancy consists of amenorrhea, vaginal bleeding, and abdominal pain. However, this triad is rare. Therefore, practitioners must suspect ectopic pregnancy in all women who present with vaginal bleeding in the first trimester until an intrauterine pregnancy is ultrasonographically documented. In only 20 % of patients with unruptured ectopic pregnancies, an adnexal mass is palpable upon pelvic examination; in the majority of these patients, physical examination findings are benign. Detection of an adnexal mass in a physical examination may be misleading, because in women with normal pregnancies, the corpus luteum may be large enough to be palpated. Many women with ectopic pregnancies have some degree of vaginal bleeding, but it is usually much less severe than that seen in women having spontaneous abortions. This bleeding results from endometrial sloughing stimulated by β-hCG produced by the ectopic trophoblast.

A patient with a suspected ectopic pregnancy should undergo several diagnostic tests. For example, once a urine pregnancy test is interpreted as positive, the serum β-hCG level should be measured. Although the majority of women with ectopic pregnancies have β-hCG levels lower than those expected for women with normal

pregnancies, a single quantitative β-hCG assessment is not diagnostic. Instead, the trend in β-hCG level identified in serial assessments frequently provides detailed information to the clinician. Normally, the β-hCG level increases from 53 % to 66 % every 48 h. If this does not occur, the pregnancy is abnormal. Inappropriate increases in the serum β-hCG level do not indicate where the pregnancy is located, just that the pregnancy is nonviable.

All patients with first-trimester vaginal bleeding should undergo transvaginal ultrasonography. A normal singleton gestation should be visualized when the serum β-hCG level approaches 2000 IU/L. Absence of a gestational sac on transvaginal sonograms when this threshold is reached should increase the suspicion of an extrauterine pregnancy. Occasionally, a "pseudogestational sac" may be seen; such sacs are usually eccentrically located in the midline. The pathognomonic ultrasonographic finding for ectopic pregnancy is a Doppler ring-enhancing ("ring of fire") mass adjacent to the ovary. In addition, free fluid in the cul-de-sac may indicate a rupture of an ectopic pregnancy.

More than three fourths of women who have ruptured ectopic pregnancies experience marked discomfort upon abdominal examination, with associated cervical motion tenderness upon pelvic examination. Complaints of shoulder pain are particularly ominous, because subdiaphragmatic irritation from hemoperitoneum manifests as referred pain. Intra-abdominal hemorrhaging can occur rapidly and be severe; as a result, hypovolemia can occur quickly. Dizziness, tachycardia, and hypotension should be evaluated immediately, and resuscitation with blood products and intravenous fluids should be initiated during preparations for transport to surgery. A number of patients will be stable enough to undergo laparoscopic salpingectomy or salpingostomy, but hemodynamically unstable patients must undergo laparotomy.

Medical management is appropriate for the majority of patients with ectopic pregnancies. Physicians have used methotrexate to treat ectopic pregnancies since 1982, with success rates reported to be as high as 94 %. Single-dose methotrexate is most effective when the initial serum β-hCG level is less than 5000 IU/L, and it may be given as a series of doses, if necessary. Absolute contraindications for treatment with methotrexate include a ruptured ectopic pregnancy; a patient who is unstable; abnormal hepatic, renal, or hematologic function; and immunodeficiency. Relative contraindications include a gestational sac larger than 3.5 cm in diameter and embryonic cardiac motion. Single-dose methotrexate is administered at 50 mg/m^2 via intramuscular injection, and the β-hCG level is checked on days 4 and 7 after treatment. The β-hCG level should decrease by 15 % from day 4 to day 7. If this decrease does not occur or the β-hCG level plateaus or increases, a second dose of methotrexate can be given. β-hCG in serum should be measured until it reaches a nonpregnant level (less than 5 IU/L).

The key to successful management of an ectopic pregnancy is early diagnosis. Physicians evaluating women of reproductive age who present with positive pregnancy tests and either vaginal bleeding or abdominal pain should have a high index of suspicion for and make vigorous efforts toward early diagnosis of an ectopic pregnancy.

Genital Tract Infections

Patients who present to the emergency room with complaints of lower abdominal pain, vaginal discharge, or fever must be evaluated for the presence of a pelvic or vulvovaginal infection. History of the present illness, a gynecologic and gastrointestinal review of systems, and sexual history should be obtained. The vulva, vagina, and cervix should be thoroughly inspected to determine if infection is present in the lower or upper genital tract, as treatment strategies differ by location. Bimanual examination should include assessment of cervical motion tenderness, adnexal pain, and pelvic masses, and the vaginal pH should be determined using litmus paper (normal adult vaginal pH, 4.0). A vaginal discharge swab should be obtained to perform microscopic review of a wet mount. To prepare the wet mount, vaginal discharge specimens are smeared onto a slide, a 2-mL drop of normal saline is applied to the slide, and a coverslip is placed on the slide. If a mycotic infection is suspected, the discharge specimen should be suspended in 10 % KOH prior to examination under the microscope. Wet mounts are diagnostic for several infections, including trichomoniasis. When appropriate, cervical cultures for *C. trachomatis* and *N. gonorrhoeae* should be obtained. Fungal, anaerobic, and aerobic cultures may be indicated for patients with recurrent or persistent infections.

Bartholin Gland Abscess

The Bartholin glands are paired structures located at the distal vagina whose ducts communicate with the vestibule between the labia minor and hymen. The ducts open at approximately the 5 and 7 o'clock positions. Obstruction of these ducts can cause Bartholin cysts, which are palpably nontender with no overlying erythema. Usually, the patient will complain of a "bulge" near her vagina. Bartholin cysts can be managed conservatively, and patients are encouraged to use sitz baths several times a day, as the warm water in these baths frequently loosens the proteinaceous material occluding the ducts. If a Bartholin cyst becomes infected, an abscess may form. Such abscesses are usually polymicrobial, with *Escherichia coli* and *Staphylococcus* species the most commonly isolated pathogens; *Chlamydia* and *Neisseria* species are rarely causative pathogens. Patients with Bartholin abscesses usually present with painful erythematous swelling adjacent to the posterior fourchette. Areas of fluctuation may be palpated at the site, and inguinal adenopathy may be present. The standard treatment of such abscesses consists of incision and drainage, which can be performed under local anesthesia. A small incision is usually sufficient to facilitate drainage of purulent material. Cultures of the abscess cavity should be obtained, and patients should begin taking an oral broad-spectrum antibiotic. A Word catheter may be placed in the abscess cavity to facilitate epithelialization of a tract independent of the Bartholin duct to prevent abscess recurrence. Rarely, Bartholin abscesses can progress to widespread cellulitis or necrotizing

fasciitis, at which point hospitalization, intravenous antibiotic administration, and surgical debridement may be necessary.

Trichomonas Vaginitis (Trichomoniasis)

Trichomoniasis is caused by the flagellated protozoan *Trichomonas vaginalis* and is the most common nonviral sexually transmitted infection (STI) in the United States. Trichomoniasis is diagnosed more often in women than in men because it tends to be asymptomatic in the latter. Symptoms include a yellow or green vaginal discharge, vaginal itching, dysuria, and dyspareunia. Upon physical examination, a frothy discharge is present, and the vaginal walls are typically erythematous. The classic strawberry cervix may be noted, which is caused by subepithelial hemorrhages. The vaginal pH is usually basic (5.0–6.5), and the discharge may be malodorous.

Trichomoniasis is definitively diagnosed using a wet mount preparation. Motile flagellated organisms in such preparations may be directly visualized under a microscope. The *T. vaginalis* microbe is larger than a white blood cell, and leukorrhea may accompany the infection. *Trichomonas* culture is rarely indicated, although an endocervical mucus specimen should be obtained and examined to rule out concurrent infection with *N. gonorrhoeae* and *C. trachomatis*.

The recommended treatment of trichomoniasis is a single 2-g dose of metronidazole (Flagyl). Side effects of this drug include nausea, metallic taste, and dark amber urine. Patients should be counseled not to consume alcohol after taking Flagyl, as it can precipitate a disulfiram-like reaction. Patients' sexual partners should undergo treatment immediately, and patients should be counseled not to engage in sexual activity until both they and their partners have received treatment to prevent reinfection.

Candidiasis

Vulvovaginal candidiasis is most often caused by *Candida albicans*. However, the incidence of infections caused by non-*albicans Candida* species has increased over the past several decades, with *Candida tropicalis* and *Candida glabrata* being the most frequently encountered species. Women at increased risk for candidiasis include those who are obese, are pregnant, have recently taken broad-spectrum antibiotics, or have a history of diabetes mellitus or immunosuppression.

Patients with candidiasis usually present with complaints of vaginal itching and a white, cottage cheese-like discharge. They may also have dysuria, burning, and dyspareunia. Physical examination reveals abundant discharge. In cases in which the infection is chronic, the vaginal mucosa may appear to be erythematous, and the vulva may be excoriated. A specimen of the discharge should be obtained, and a wet

mount of the specimen with a 10 % KOH solution should be prepared and examined. Microscopically, pseudohyphae and yeast buds may be visualized.

A number of over-the-counter antifungals are available for treatment of candidiasis, including clotrimazole and miconazole, which should be applied vaginally. In addition, a single 150-mg oral dose of fluconazole is effective. In cases of recurrent or persistent yeast infection, fungal cultures should be obtained, because routinely used azoles are less effective at eradicating infections caused by non-*albicans Candida* species than at eradicating those caused by *C. albicans*.

Bacterial Vaginosis

Bacterial vaginosis (BV) is a clinical syndrome resulting from a shift from the normal *Lactobacillus* species-dominated vaginal environment to one with overgrowth of anaerobic bacteria, *Gardnerella vaginalis*, and *Mycoplasma hominis*. Although BV is not considered to be sexually transmitted, many risk factors for the disease are associated with sexual activity, including early age at first coitus and multiple sexual partners. Other risk factors include cigarette smoking, douching, and sex during menses.

Patients usually present with complaints of a copious, malodorous vaginal discharge that is usually gray in color. Upon physical examination, discharge in the vaginal vault without vaginal wall erythema is noted. The Centers for Disease Control and Prevention (CDC) established four diagnostic criteria for BV, three of which must be fulfilled for a definitive diagnosis: (1) a homogeneous white discharge that coats the vaginal walls, (2) clue cells detected via microscopic examination of a discharge specimen, (3) vaginal pH greater than 4.5, and (4) a fishy odor of the vaginal discharge with application of 10 % KOH solution (whiff test) (Centers for Disease Control and Prevention 2006).

Treatment of BV consists of 500 mg of oral Flagyl taken twice daily. Alternative therapies include a vaginal metronidazole gel or clindamycin cream. Treatment of BV is important, as it has been associated with infections that develop after genital tract surgery, including hysterectomy and surgical abortion. Patients with recurrent BV should be screened for STI with other pathogens, including *C. trachomatis* and *N. gonorrhoeae*.

Herpes Simplex Virus Infections

An estimated 3.8 % of Americans were diagnosed with herpes simplex virus (HSV) infection from 1999 to 2004. Genital herpes infections are predominantly caused by type 2 HSV, whereas up to 10 % may be caused by type 1 HSV. Patients who have had oral infections (type 1) may have some protection against subsequent genital infections (type 2). HSV enters sensory nerve endings and undergoes retrograde

axonal transport to dorsal root ganglia, where it remains for life. The virus may remain latent; be subsequently reactivated, complete with active, painful lesions; or be shed from the skin asymptomatically.

Primary HSV infection is active in about 70 % of affected women, and symptoms usually develop within 7 days after the first exposure to the virus. Symptoms may include vulvovaginal burning, dysuria, and pain. Primary infections may be accompanied by more systemic symptoms, including malaise and low-grade fever. Vesicular lesions occur first and will subsequently rupture, causing ulcers. These ulcers are shallow and exquisitely painful and may be surrounded by areas of erythema. The lesions usually heal within 10 days. Recurrent outbreaks are typically less severe than the original ones and may be accompanied by a prodrome in up to two thirds of patients. Prodromal symptoms include paresthesia, which may feel like tingling or itching in an area where lesions erupt.

The gold standard for diagnosis of HSV is tissue culture. HSV IgG serologic tests may be ordered, but they provide no information about the timing of the infection. If HSV infection is suspected clinically, treatment should be initiated promptly.

Acyclovir, famciclovir, and valacyclovir are all currently recommended by the CDC for treatment of active HSV infections. In general, treatment should be administered for 10 days, but it may be extended if lesions remain. Suppressive therapy should be considered for women who have frequent recurrences (at least 6 per year), as this therapy has reduced the frequency of recurrent outbreaks by 70–80 %. Pregnant women also should be considered candidates for suppressive therapy to reduce the likelihood of fetal HSV transmission. If active lesions are present during labor, a cesarean delivery is necessary to prevent neonatal infection.

Syphilis

Syphilis is caused by *Treponema pallidum*, a motile anaerobic spirochete that invades moist but intact mucosa. From 2007 to 2008, the total number of syphilis cases reported to the CDC increased 13.1 % to 46,277, and the incidence in women increased 36.4 % to 1.5 cases per 100,000 individuals. Risk factors for syphilis include low socioeconomic status, young age, early onset of sexual activity, and multiple sexual partners.

Untreated syphilis has a progressive course. About 10–60 days after a spirochete comes in contact with the vulva, vagina, or cervix, a primary syphilitic chancre develops. This chancre is a nontender ulcer with a punched-out base and raised borders. Painless inguinal adenopathy may be present, as well. The chancre has a high concentration of spirochetes and is therefore highly infectious. Without treatment, the chancre will heal spontaneously in 6 weeks. An exudate from the chancre can be examined for the presence of spirochetes under a dark field microscope to assist in diagnosis. In addition, 2 nontreponemal serologic tests can be performed: the Venereal Disease Research Laboratory and rapid plasma reagin tests. These tests are useful for population screening for and assessing response to treatment of syphi-

lis. However, a fluorescent treponemal antibody-absorption test or *T. pallidum* particle agglutination assay should be used to confirm a diagnosis of syphilis in a patient with positive nontreponemal serology.

Systemic manifestations of secondary syphilis usually develop about 6–10 weeks after the chancre disappears. The hallmark of this phase is a diffuse maculopapular rash on the palms and soles. Condyloma lata, which are pink or gray-white cutaneous plaques, may also develop. Like the chancre described above, condyloma lata have high spirochete loads and are highly infectious. Malaise, headache, anorexia, fever, arthralgia, and meningitis also may occur during the secondary syphilis phase.

If the patient does not receive treatment, she is at risk for tertiary syphilis. In fact, the late stages of syphilis develop in about 15 % of untreated patients. Tertiary syphilis may not develop for up to 20 years after the development of secondary syphilis and is characterized by multiorgan dysfunction, including cardiac and musculoskeletal abnormalities. In addition, neurologic changes are associated with tertiary syphilis, including difficulty coordinating muscle movements, paralysis, ataxia (the "syphilis shuffle"), gradual blindness, and dementia. Gummas, which are granulomatous-like growths, may develop in a number of tissues, including the vulva.

T. pallidum is exquisitely sensitive to penicillin, and the standard treatment of both primary and secondary syphilis is a single injection of 2.4 million U of benzathine penicillin. Tetracycline derivatives may be used in patients who are allergic to penicillin. Patients should undergo follow-up and assessment of their Venereal Disease Research Laboratory and rapid plasma reagin test results. If the titer increases, either the treatment has failed, or the patient has experienced reinfection and should receive treatment again. The standard treatment of tertiary syphilis is weekly penicillin for 3 weeks or doxycycline for 4 weeks. Unfortunately, treatment of tertiary syphilis may not reverse its clinical sequelae.

Chlamydial Infection

C. trachomatis is an obligate intracellular pathogen that is completely dependent on host cells for survival. Infections with *C. trachomatis* make up the largest proportion of STIs reported to the CDC, and an estimated 4.2 % of young adults in the United States are infected with it. *C. trachomatis* infects the columnar cells of the endocervix, resulting in a mucopurulent discharge in patients with symptomatic infections. The majority of infections are asymptomatic, however, so physicians are encouraged to screen women younger than 25 years old and those at high risk for STIs for *C. trachomatis* infection.

Typical symptoms of chlamydial infection include vaginal discharge and dysuria. The cervix may appear erythematous, and the discharge can be visualized at the cervical os. Examination of a wet mount specimen of the discharge typically reveals more than 10 white blood cells per high-power field. Also, endocervical

specimens may be submitted to culture or enzyme-linked immunosorbent assay analysis.

All patients with a clinical picture suggestive of *C. trachomatis* infection should receive treatment immediately. The standard treatment is 1 g of oral azithromycin taken once or 100 mg of oral doxycycline taken twice daily for 7 days. If symptoms do not resolve after several weeks of treatment, the patient should undergo a test of cure. Furthermore, her sexual partner should undergo treatment prior to resumption of sexual activity.

Gonorrhea

N. gonorrhoeae is a gram-negative coccobacillus that infects columnar and transitional epithelial cells, resulting in suppurative cervicitis. In 2008, the incidence of gonorrheal infection in American women was 119.4 per 100,000 individuals. Like chlamydial infection, gonorrhea may be asymptomatic. When it is symptomatic, typical manifestations include a white or yellow vaginal discharge without odor. Scant vaginal bleeding may occur, as may dysuria and dyspareunia. Upon physical examination, erythema and injection of the cervix are present as well as a purulent discharge from the cervical os. A wet mount analysis of the discharge usually reveals more than 10 white blood cells per high-power field. Nucleic acid amplification tests for the detection of gonococcal DNA are frequently used for diagnosis.

About 35 % of women with gonorrhea are co-infected with *C. trachomatis*. Therefore, all women with gonococcal cervicitis should receive treatment of both infections. Treatment of gonorrhea consists of a single intramuscular injection of 125 mg of ceftriaxone. Quinolones have been efficacious in treating gonorrhea. However, because of increasing bacterial resistance to quinolones in certain regions of the country, the CDC has advised against quinolone-based treatment of gonococcal infections. A test of cure is not necessary if symptoms resolve, but patients should be advised to remain abstinent until their sexual partners undergo treatment.

PID

PID is an acute infection of the upper genital tract in women. Associated with both gonorrhea and *C. trachomatis* infection, PID is likely polymicrobial in nature, and the associated changes in the genital structures of affected women generally result from exaggerated inflammatory responses. PID has a number of well-established risk factors, including young age, low socioeconomic status, multiple sexual partners, and early age at first coitus. More than 600,000 women receive treatment of acute PID annually, so this infection is a significant public health burden. Although

STI screening efforts have reduced the number of women with PID, it remains a source of significant morbidity in women who have it.

PID is not always symptomatic. In fact, asymptomatic infections are likely responsible for diagnoses of tubal infertility. In women who present with symptoms, lower abdominal pain is common. Vaginal discharge, abnormal uterine bleeding, dysuria, fever, and nausea also may be present. Symptoms usually develop either during or immediately after menstruation.

The CDC has set strict diagnostic criteria for PID. At minimum, cervical motion and uterine or adnexal tenderness must be present. Other examination findings increase the diagnostic specificity for PID, including (1) an oral temperature greater than 101 °F (38.3 °C), (2) abnormal cervical or mucopurulent discharge, (3) high numbers of white blood cells in vaginal secretions detected using saline microscopy, (4) an elevated erythrocyte sedimentation rate or C-reactive protein level, and (5) laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*. The gold standard for diagnosis of PID is direct visualization of inflamed fallopian tubes or other pelvic structures. This is rare in practice, however. Abdominal pain may preclude a thorough pelvic examination. In such cases, transvaginal ultrasonography should be considered to detect an adnexal pathology, specifically, a tubo-ovarian abscess. Although a patient's medical history and physical examination may suggest PID, ruling out other causes of lower abdominal pain, including appendicitis and diverticulitis, is important.

Once PID is diagnosed, the appropriateness of inpatient versus outpatient treatment must be determined. In general, patients should be hospitalized if any of the following criteria are met: (1) a surgical emergency (e.g., appendicitis) cannot be definitively excluded; (2) the patient is pregnant; (3) the patient is unable to tolerate oral therapy; (4) the patient has a severe illness, nausea and vomiting, or a high fever; and (5) the patient has a tubo-ovarian abscess. The CDC recommendations for treatment of PID are shown in Table 15.2. Patients who can receive outpatient treatment must undergo a follow-up examination within 72 h. Those who have no clinical responses to treatment should be hospitalized. Researchers have shown that women who undergo treatment of PID as outpatients take as little as 70 % of their prescribed medication, so patients should be strongly counseled to adhere to their medication regimens and provide hospital contact information should they have questions regarding their antibiotics. Surgery is rarely required for PID even when a tubo-ovarian abscess is present.

Rescreening for gonorrhea and chlamydial infection is recommended 4–6 weeks after completion of therapy for PID. In addition, all women diagnosed with acute PID should be tested for human immunodeficiency virus infection. Male sexual partners of patients with PID should undergo examination and treatment if they have had sexual contact within 60 days of the patient's diagnosis. Treatment in these men consists of antimicrobial agents typically used against gonorrhea and chlamydial infection.

Table 15.2 CDC guidelines for treatment of PID

Recommended treatment	Alternative treatment
Hospitalized patients	
Cefotetan 2 g IV every 12 h OR Cefoxitin 2 g IV every 6 h PLUS Doxycycline 100 mg orally or IV every 12 h until improvement followed by doxycycline 100 mg orally BID to complete 14 days of treatment[a]	Clindamycin 900 mg IV every 8 h PLUS Gentamicin 2-mg/kg loading dose IV or IM followed by 1.5 mg/kg IV every 8 h until improvement followed by doxycycline 100 mg orally BID to complete 14 days of treatment[a]
Nonhospitalized patients	
Levofloxacin 500 mg orally once daily for 14 days[b] OR Ofloxacin 400 mg orally BID for 14 days[b] WITH OR WITHOUT Metronidazole 500 mg orally BID for 14 days	Ceftriaxone 250 mg IM in a single dose PLUS Doxycycline 100 mg orally BID for 14 days WITH OR WITHOUT Metronidazole 500 mg orally BID for 14 days

Based on data from Centers for Disease Control and Prevention et al. (2006)
IV intravenously, *IM* intramuscularly, *BID* twice daily
[a]In cases with tubo-ovarian abscesses, concomitant oral administration of metronidazole or clindamycin may be considered to increase anaerobic coverage
[b]Quinolone antibiotics should not be given to women with a history of or recent foreign travel or whose sexual partners have recently traveled abroad or in areas with documented quinolone-resistant *N. gonorrhoeae* infections

Vaginal Fistula

Symptoms of an abnormal connection between the vagina and either the bladder or colon can be very distressing for a patient. Vesicovaginal and rectovaginal fistulae are rare, but they are significant complications of underlying disease, trauma, or therapy.

The most common cause of vesicovaginal fistulae in developing countries is birth trauma, specifically, compression of the bladder against the fetal head owing to obstructed labor. In developed countries, abdominal hysterectomy is the most common cause of vesicovaginal fistulae, with an incidence of 1 case per 1800 hysterectomies. Thus, physicians must have a high level of suspicion for this postoperative complication in patients who have undergone hysterectomy. Other etiologies of vaginal fistulae include trauma, foreign body erosion, and pelvic irradiation. Patients with these fistulae typically complain of leakage of urine through the vagina. Such leakage may be difficult to detect in a pelvic examination, but retrograde filling of the bladder with normal saline dyed with indigo carmine and visualization of blue fluid in the vagina are diagnostic. Patients with vesicovaginal fistulae should also undergo intravenous pyelography or computed tomography (CT) scans to rule out ureterovaginal fistulae. Surgical management of these fistulae is preferred over

other treatments but may not be feasible in irradiated patients. In such cases, placement of percutaneous nephrostomy tubes or urinary diversion should be considered.

Rectovaginal fistulae are most often caused by diverticular disease, although inflammatory bowel disease and pelvic irradiation are also well-described predisposing factors for these fistulae. Radiation-induced fistulae most often involve the distal sigmoid and rectum, and recurrent cancer in such fistulae must be excluded. Passage of stool from the vagina is diagnostic for rectovaginal fistulae, and patients should undergo CT scans of the abdomen and pelvis with rectal contrast to best identify the site of fistula origination. Spontaneous closure of a rectovaginal fistula is rare, and surgical closure is preferred over observation, if possible. For patients with malignancies who have received radiation therapy, palliation of a rectovaginal fistula using a colostomy may be the only option. A patient with an identified rectovaginal fistula must be referred immediately to a surgeon, as treatment of it is usually multidisciplinary.

Ovarian Torsion

Ovarian torsion occurs when the ovary twists on the infundibulopelvic ligament, which contains the ovarian vessels, resulting in impeded blood flow. The majority of cases of ovarian torsion are associated with benign cysts or neoplasms, which provide torque for the ovary to swing on its vascular pedicle. In general, the larger the adnexal mass, the greater the risk of ovarian torsion, and researchers have shown that the majority of masses in ovarian torsion cases are at least 5 cm in diameter. Obstruction of the infundibulopelvic ligament causes greater occlusion of venous and lymphatic outflow from the ovary than the arterial supply feeding it, thereby making the ovary edematous and hyperemic when torsion is present. More than 80 % of cases of ovarian torsion occur in women younger than 50 years.

Patients with ovarian torsion usually have acute-onset unilateral lower abdominal pain that is frequently accompanied by nausea and vomiting. The patient may report an association between some type of activity and onset of pain, and the pain can wax and wane or change with position. Upon physical examination, an adnexal mass is palpable in 72 % of women, although the examination may be limited because of pain. The patient may have an acute abdomen, and hematologic laboratory examination may reveal leukocytosis. In such cases, acute appendicitis must be ruled out. Ultrasonographic evaluation may demonstrate an adnexal mass. Although use of Doppler ultrasonography to confirm the presence or absence of blood flow to the affected ovary is advocated for diagnosis of ovarian torsion, torsion may occur in ovaries without sonographically documented interruption of the vascular supply. As with all women at reproductive age with abdominal pain, an ectopic pregnancy must be excluded.

The standard treatment of ovarian torsion is surgery, and laparoscopy and laparotomy are acceptable surgical approaches. Detorsion may be performed even if the

ovary appears to be nonviable, particularly in young women who desire to preserve their fertility. Excision of the ovary and/or fallopian tube is also acceptable. The risk of pulmonary embolism following detorsion is small, and the actual incidence of pulmonary embolism following detorsion is low in these patients.

Key Practice Points

- When possible, chemotherapy and radiation therapy for cancer in a pregnant patient should be delayed until the second or third trimester.
- Most radiologic procedures will not adversely affect a developing fetus. Regardless, pregnant patients should be counseled about the risk to the fetus prior to imaging.
- Pregnancy status should be determined for all reproductive-age women who present with vaginal bleeding or abdominal pain.
- The first priority in patients with acute vaginal bleeding is ensuring hemodynamic stability.
- Ruptured ectopic pregnancy and ovarian torsion are surgical emergencies requiring immediate consultation with an obstetrician/gynecologist.
- Identifying genital tract infections and initiating appropriate treatment of them are important to prevent sequelae and comorbidities associated with these infections.
- All sexual partners of women diagnosed with STIs should be referred to an STI clinic for evaluation and treatment.

Suggested Readings

American College of Obstetricians and Gynecologists. Committee Opinion Number 299: Guidelines for diagnostic imaging during pregnancy. 2004.

American College of Obstetricians and Gynecologists. Practice Bulletin Number 82: Management of herpes in pregnancy. 2007.

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Chapter 16
Dermatologic Emergencies

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Contents

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Chapter Overview

Patients present to the emergency rooms at cancer centers with a wide spectrum of skin diseases. These diseases include drug reactions, primary cutaneous infections, inflammatory skin disorders (such as Sweet syndrome), graft-versus-host disease (GVHD), and skin signs of disseminated infections. This chapter covers four skin disorders that each have a high associated morbidity: toxic epidermal necrolysis (TEN), drug hypersensitivity syndrome (now known as drug reaction with eosinophilia and systemic symptoms [DRESS]), necrotizing fasciitis, and cutaneous GVHD. With the exception of GVHD, these disorders occur as frequently in the mildly immunosuppressed host as they do in the severely immunosuppressed.

Introduction

We will discuss four skin disorders that occur in the oncology population and have a high associated morbidity. Reaching a correct clinical diagnosis is not difficult when patients present with these disorders in their mature stage. By that point, however, successful therapy may be more challenging. The early skin signs (and other early signs) of these disorders are often not specific and may not allow for definitive diagnosis. They should, however, prompt the clinician to at least hold the patient for further evaluation.

Stevens-Johnson Syndrome and TEN

TEN is a severe mucocutaneous drug reaction. Affected patients slough off a large portion of their skin and have erosive damage to their lips and oral mucosa. Stevens-Johnson syndrome (SJS) is a milder form of TEN. Patients with SJS have severe oral mucosal disease but slough off a much smaller portion of their skin. The mortality rate for SJS is also lower than that for TEN. In some patients, SJS evolves into TEN. We refer to these two related disorders as SJS-TEN.

SJS has an approximate annual incidence of six cases per million persons, whereas that of TEN is one case per million persons. TEN and SJS are almost always caused by medications; other occasional reported causes include vaccinations, bacterial infections, and idiopathies. Drugs that are commonly associated with SJS-TEN

Table 16.1 Drugs associated with SJS-TEN

High-risk
Allopurinol
Carbamazepine
Lamotrigine
Nevirapine
Oxicam nonsteroidal anti-inflammatory drugs (e.g., piroxicam)
Phenobarbital
Phenytoin
Sulfasalazine
Sulfonamide antibiotics
Significant but lower risk
Acetic acid nonsteroidal anti-inflammatory drugs (e.g., diclofenac)
Other antibiotics (aminopenicillins, cephalosporins, macrolides, quinolones, tetracyclines)

Based on data from Halevy S, Ghislain PD, Mockenhaupt M, et al. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J Am Acad Dermatol* 2008;58:25–32

Table 16.2 Chemotherapeutic agents that have caused 1 or more episodes of SJS-TEN

Asparaginase	Gemcitabine with radiation therapy
Bleomycin	Imatinib mesylate
Chlorambucil	Interleukin-2
Cytarabine	Methotrexate
Docetaxel	Mithramycin
Doxorubicin	Rituximab
Etoposide	Suramin
Fludarabine	Thalidomide

Based on data from Mays SR, Kunishige J. Cutaneous reactions to medications. In: Yeung SCJ, Escalante CP, Gagel RF, eds. *Medical Care of Cancer Patients*. Shelton, CT: B.C. Decker; 2009:617–627

are listed in Table 16.1. The most frequent culprits are antibiotics, anticonvulsants, antiretrovirals, nonsteroidal anti-inflammatory drugs, and allopurinol.

In general, physicians' knowledge of SJS-TEN is derived from cases caused by conventional medications. However, chemotherapeutic agents can also rarely cause SJS-TEN. Table 16.2 lists chemotherapeutic agents that were identified as causes of SJS-TEN in case reports from 1978 to 2003. Each agent has only one or two reports of associated SJS-TEN. SJS-TEN that occurs in the setting of chemotherapy seems to be very idiosyncratic.

Clinical Features

The onset of SJS-TEN typically occurs 7–21 days after the first exposure to the causative medication. In a review of 69 cases of TEN, 78 % occurred within 3 weeks after exposure (Stern and Chan 1989). For certain drugs, such as phenytoin, the onset may take 8 weeks or more. However, re-exposure to a causative medication may result in the onset of SJS-TEN within 48 h.

A prodrome with high fever, sore throat, myalgia, and malaise precedes the skin disease by up to 3 days. Afterward, painful red patches suddenly appear on the trunk and subsequently on the face and proximal extremities. The palms and soles but usually not the distal extremities may be involved. The presence of many tender red patches on the trunk and proximal extremities is highly suggestive of incipient TEN. The patches become grey and start to form fragile blisters; the blister roofs then slide off the skin, leaving behind large, moist erosions (Fig. 16.1).

Classification of the patient's condition depends upon measurement of the detached and detachable epidermis.

- SJS: <10 % of body surface area (BSA)
- TEN: >30 % of BSA
- SJS-TEN overlap: 10–30 % of BSA

Most patients with SJS-TEN have oral mucosal disease. The initial symptoms are burning of the lips and buccal mucosa. Blisters then appear on the lips and

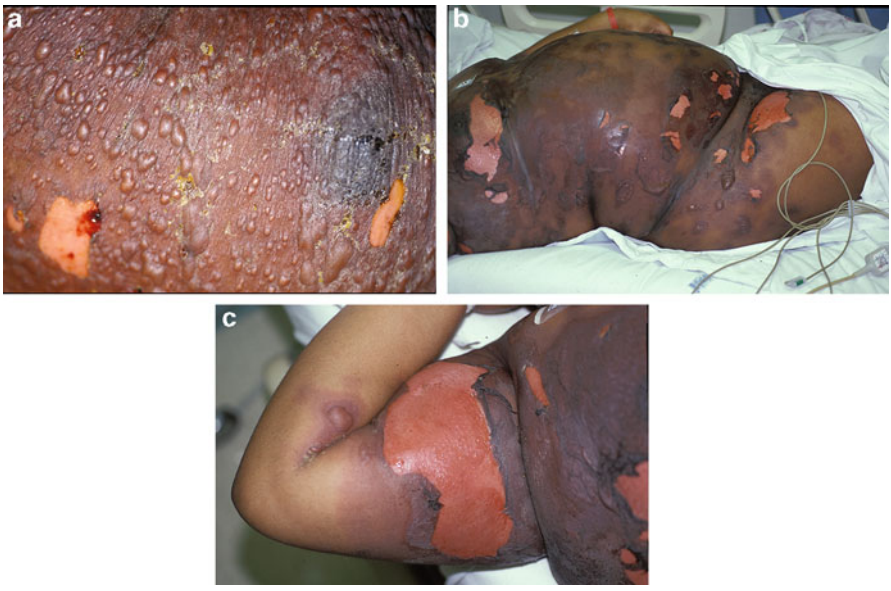

Fig. 16.1 (**a**) Tense blisters and erosions in a patient with TEN. (**b**) Large erosions in a patient with TEN. (**c**) Close-up of a large erosion and intact blister

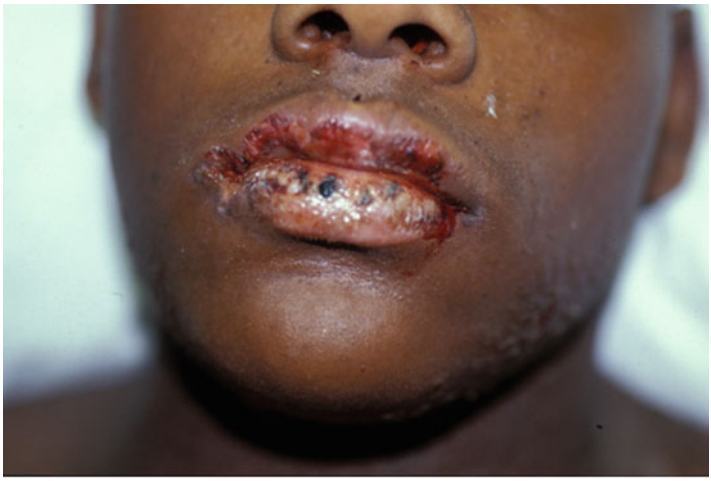

Fig. 16.2 Erosion and crusting of the lips in a patient with TEN

buccal mucosa and sometimes on the palate, gingiva, tongue, and pharynx. These blisters rupture quickly, leaving painful erosions that prevent the patient from eating or drinking. The lips become covered in hemorrhagic crusts (Fig. 16.2). The onset of oral mucosal disease may occur concurrently with the skin disease or precede it by a few days. Patients with SJS-TEN may also develop painful erosions at almost any mucosal site, including the eyes, nostrils, esophagus, bronchi, genitals, and anus.

During the initial active phase of SJS-TEN, the patient has persistent fever, formation of mucocutaneous blisters, and partial shedding of the skin and oral mucosa. The active phase is complete when no new blisters appear. At about this time, the extent of skin detachment reaches its peak. If the patient is no longer receiving the causative medication, the active phase lasts 5 days. Barring other complications, the eroded skin then slowly re-epithelializes over the next 2–3 weeks. Mucosal sites take longer to heal than skin sites.

Complications

Patients with TEN have very large cutaneous erosions that may persist for 2–3 weeks. As a result of a compromised skin barrier, these patients may develop bacteremia, especially with *Staphylococcus aureus* or *Pseudomonas* species. This is the main cause of death in patients with TEN. *Candida* fungemia also may occur. The extensive loss of the skin barrier also predisposes patients to dehydration, electrolyte abnormalities, and hypothermia. These complications are much less common in patients with SJS.

Other possible complications of SJS-TEN are pneumonia, infected catheters, and partial or complete loss of vision owing to ocular erosions and scarring.

Prognosis

The overall mortality rate for SJS is 5 %, whereas that for TEN is 30 %. The severity-of-illness score for TEN (SCORTEN) is a predictor of disease severity and mortality based on a 7-point checklist. Patients are evaluated for clinical/laboratory parameters such as age greater than 40 years and extent of epidermal detachment (Table 16.3). The more adverse prognostic factors present, the worse the predicted mortality rate.

Prompt discontinuation of a causative drug reduces the risk of death in SJS-TEN patients by about 30 % per day. An episode of SJS-TEN caused by a drug with a long half-life is more likely to end in death than one caused by a drug with a short half-life.

Diagnosis

The clinical presentation of an established case of SJS-TEN is characteristic. The patient has fever; painful oral mucositis; hemorrhagic crusts on the lips; painful red patches, especially on the trunk; fragile blisters; and cutaneous erosions. This presentation often occurs within 7–21 days of receiving a drug associated with SJS-TEN. Incipient SJS-TEN may be suspected in a patient who presents with an early morbilliform eruption and any tenderness of the oral mucosa or skin.

Table 16.3 Severity-of-illness score for TEN variables

Variable	Weight
Age ≥40 years	1
Malignancy	1
BSA detached ≥10 %	1
Tachycardia ≥120/min	1
Serum urea level ≥27 mmol/L	1
Serum glucose level ≥250 mmol/L	1
Serum bicarbonate level <20 mmol/L	1

Based on data from Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: A severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000;115:149–53

Skin biopsy for routine histology reveals substantial or full-thickness necrosis of the epidermis, a subepidermal split, and a sparse inflammatory infiltrate in the dermis. These findings are not specific.

Once SJS-TEN is diagnosed, the next step is to identify the causative medication. We have found that using a drug calendar can be very helpful. The culprit is usually not one of the patient's chronic medications but rather a drug that has been given for the first time in the 3-week period prior to the onset of SJS-TEN. However, if a patient is re-exposed to a causative drug, the reaction may occur within 48 h. A review of the literature also helps to identify those drugs that are commonly associated with SJS-TEN.

A medication is probably not the trigger for SJS-TEN if it was first given within the previous 24 h or if the duration of treatment exceeds 3 weeks. An exception to this is with anticonvulsant medications (especially phenytoin), which may take up to 8 weeks to cause SJS-TEN.

Differential Diagnosis

Staphylococcal scalded skin syndrome (SSSS) may clinically resemble SJS-TEN. Patients with both disorders are febrile and have widespread tender erythema and erosions. The erosions of SSSS are more superficial than those of SJS-TEN. In addition, patients with SSSS do not have oral mucosal disease. When we suspect either of these diseases, we perform a skin biopsy on the edge of a blister for rapid (frozen) section. A pathology department can report the results in only a few hours. Frozen sections reliably differentiate between SJS-TEN (subepidermal split) and SSSS (intraepidermal split).

Grade IV (severe) acute cutaneous GVHD often resembles TEN both clinically and histologically. Differentiating between the two disorders can be nearly impossible. Also included in the differential diagnosis are paraneoplastic pemphigus and linear IgA disease.

Therapy

An important initial step in treating SJS-TEN is discontinuation of the offending drug. If the offending drug cannot be reliably identified, then all nonessential medications should be withdrawn.

TEN patients have extensive skin detachment with water, electrolyte, and protein loss: they physiologically resemble burn patients. There is some evidence that admission to a burn unit (not to a general intensive care unit) leads to improved outcomes (Endorf et al. 2008).

Treatment of TEN is primarily supportive: the goal is to protect the skin while it heals and correct any fluid and nutritional deficiencies. Intravenous fluid and electrolyte replacement in TEN patients is important, as insensible water loss may

be significant. TEN patients need nutritional support because of a hypermetabolic state, wound exudative losses, and their inability to eat. Pain management and thermoregulation are also important. An ophthalmologist should evaluate patients with any evidence of ocular involvement.

TEN patients are at high risk for skin colonization by pathogenic bacteria with subsequent bacteremia owing to the compromised skin barrier. Patient care is therefore performed in a sterile fashion, and the patient may receive daily hydrotherapy with chlorhexidine gluconate or another antiseptic agent.

Another goal of skin care is to protect the large cutaneous erosions while re-epithelialization occurs. Some centers use synthetic skin substitutes such as silicone film embedded in nylon mesh (Biobrane), whereas others use porcine xenografts or human skin allografts. Physicians also take different approaches to the care of the patches of necrotic epidermis: some centers debride them surgically or with hydrotherapy, whereas others leave them in place.

TEN patients usually remain in the burn unit until re-epithelialization is almost complete and until they are otherwise stable. The median burn unit stay in one series of 19 patients was 14 days (Gerdts et al. 2007). Practical guidelines for the management of patients with TEN are available (Fromowitz et al. 2007).

Investigators have evaluated various pharmacologic agents in an attempt to halt progression of TEN. These agents include systemic steroids, cyclosporine, and intravenous immunoglobulins (IVIGs). With one exception (thalidomide, which produced a negative result), investigators have not performed randomized controlled trials of these agents. A large retrospective study ($n=281$) did not demonstrate a clear benefit of treatment of SJS-TEN with either systemic steroids or IVIG (Schneck et al. 2008).

The most intensively studied of these pharmacologic agents is IVIG. In SJS-TEN patients, the destruction of the epidermis is caused by massive apoptotic cell death of keratinocytes via intracellular signaling proteins. One implicated pathway involves binding of the FAS ligand to the keratinocyte death receptor FAS. In vitro, pooled IVIG (which contains anti-FAS ligand antibodies) halted subsequent keratinocyte necrosis. Later, some clinical case studies demonstrated an improved mortality rate in TEN patients given IVIG, whereas others found no improvement (Abood et al. 2008).

The literature contains individual case reports in which patients with SJS-TEN almost certainly benefitted from receiving IVIG (Hebert and Bogle 2004). IVIG is less toxic than systemic steroids; some clinicians therefore feel that the current clinical and laboratory evidence is sufficiently compelling to justify its use, especially given the morbidity and mortality associated with TEN. The purpose of any medical therapy for TEN is to halt progression of the blistering process before it becomes extensive. Therefore, early initiation of this therapy is important.

Drug Reaction with Eosinophilia and Systemic Symptoms

DRESS is a severe nonblistering drug reaction. The typical findings are fever, a maculopapular skin eruption, lymphadenopathy, hepatitis, and a peripheral eosinophilia. The hepatitis may be severe and may be the cause of death; other internal

Table 16.4 Drugs associated with DRESS

Abacavir
Allopurinol
Carbamazepine
Dapsone
Lamotrigine
Minocycline
Nevirapine
Phenobarbital
Phenytoin
Sulfasalazine
Trimethoprim-sulfamethoxazole

Based on data from:
Ben m'rad M, Leclerc S, Blanche P. et al. Drug-induced hypersensitivity syndrome. Medicine. 2009;88:131–40
Eshki M, Allanore L, Musette P, et al. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: A cause of unpredictable multiorgan failure. *Arch Dermatol*. 2009;145:67–72

organs are sometimes affected as well. In the early stage of DRESS, patients may simply appear to have an uncomplicated maculopapular drug eruption.

Another name for DRESS is drug hypersensitivity syndrome. Phenytoin (Dilantin) hypersensitivity syndrome, anticonvulsant hypersensitivity syndrome, and dapsone hypersensitivity syndrome are all probably subtypes of DRESS.

In general, the most common causes of DRESS are anticonvulsants, sulfonamide antibiotics, minocycline, allopurinol, and certain antiretroviral medications (Table 16.4). The incidence of DRESS caused by anticonvulsants and sulfonamides ranges from 1 in 1000 to 1 in 10,000 exposures.

Clinical Features

The onset of DRESS typically occurs 2–6 weeks after the first exposure to the causative medication. Patients may experience a prodrome of high fever, malaise, and sore throat that precedes the onset of the rash by a few days. At least 70 % of patients with DRESS have fever (temperature greater than 37.5 °C) during the disease course. The most clinically striking feature of DRESS is the rash, a pink or red maculopapular eruption that starts on the face and upper trunk (Fig. 16.3). The rash then progresses caudally to involve the entire trunk and thighs. This eruption occasionally progresses to erythroderma or TEN.

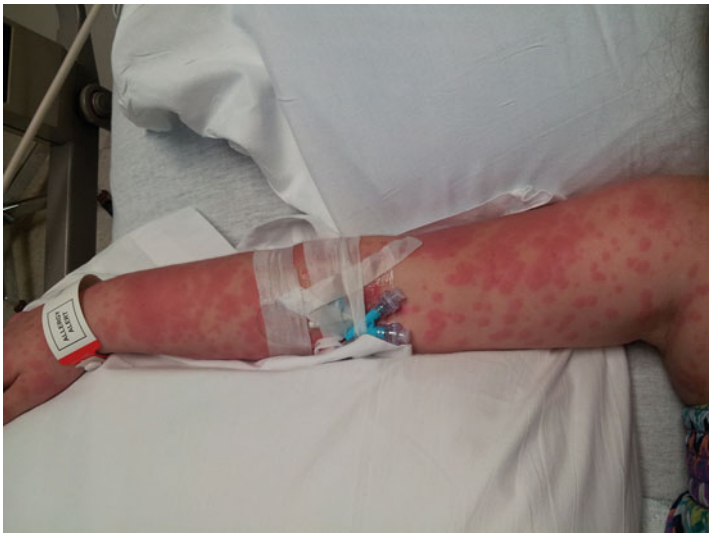

Fig. 16.3 Morbilliform eruption on the arm in a patient with DRESS

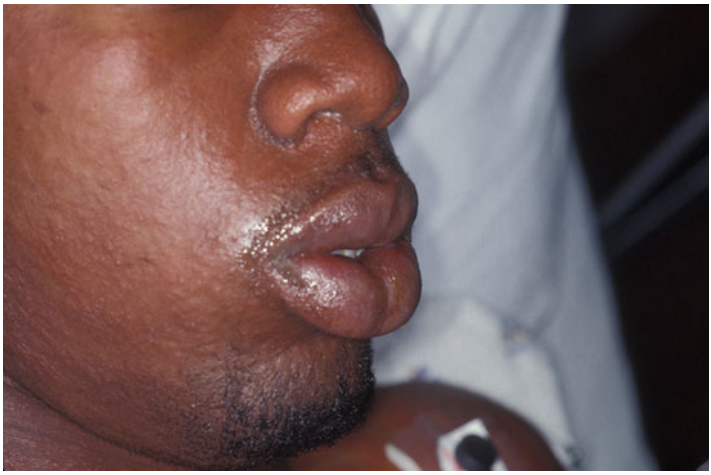

Fig. 16.4 Lip edema in a patient with DRESS

Some patients with DRESS have very characteristic periorbital or lip edema that is not associated with laryngeal edema (Fig. 16.4). The facial edema may distort facial features and occurs in 30–50 % of patients with DRESS. The majority of patients develop mild mucosal involvement such as small lip erosions or redness of the conjunctiva and oral mucosa. Many also have tender lymphadenopathy of the neck, axillary, or inguinal lymph node basins.

Most patients with DRESS develop drug-induced hepatitis of variable severity. Some have elevated transaminase levels without any clinical sequelae. In one series

of 27 patients, 96 % had elevated transaminase levels, with 50 % having marked elevation (greater than 10 times normal) (Ang et al. 2010). Patients may have palpable hepatomegaly. Some patients develop hepatic necrosis and liver failure, the most common cause of death related to DRESS. The degree of hepatitis is partially related to the interval between the onset of the syndrome and discontinuation of the drug.

Internal organ involvement may occur 1–4 weeks after the rash develops. Renal disease occurs in less than 20 % of DRESS patients and varies from mild hematuria through nephritis to acute renal failure. Other serious, but less common, complications include pneumonitis, myocarditis, and encephalitis.

Most DRESS patients have hematologic abnormalities. In two case studies, at least 80 % had these abnormalities (Ben m'rad et al. 2009; Ang et al. 2010). The most common hematologic abnormalities are eosinophilia, leukocytosis, lymphopenia, and atypical circulating lymphocytes.

The clinical and laboratory features of DRESS are variable, with no one feature being uniformly present. For example, 10 % of patients lack even the characteristic rash. Proposed diagnostic criteria are available (Ang et al. 2010).

Prognosis

Most patients with DRESS ultimately have a favorable outcome However, the skin disease, fever, and hepatitis may wax and wane for months before eventually resolving. Some patients have liver failure and need transplantation. The approximate overall mortality rate for DRESS is 10 %, mainly because of liver disease. Renal disease may be severe and require prolonged dialysis. Other occasional causes of mortality and severe morbidity in DRESS cases include pneumonitis, heart failure, encephalitis, and pancytopenia. Autoimmune thyroiditis may occur during the subsequent months, and thyroid function should be intermittently evaluated during that time.

Diagnosis

The diagnosis of DRESS should be suspected in any patient who presents with a widespread maculopapular eruption, fever, palpable lymphadenopathy, facial edema, elevated transaminase levels, and/or marked eosinophilia. With good reason, such patients are often suspected of having a systemic infection, especially a viral exanthem, and are evaluated accordingly. However, the failure to consider DRESS in the differential diagnosis sometimes leads to failure to discontinue the offending medication and, thus, to disease progression.

Skin biopsy demonstrates keratinocyte necrosis, basal cell vacuolar degeneration, a perivascular lymphocytic infiltrate, and dermal eosinophils. These findings are not specific.

Laboratory findings can be supportive in making the diagnosis of DRESS. These should evaluate for hematologic, renal, and hepatic function, so they should include at least a comprehensive metabolic panel, urinalysis, and complete blood count with differential. These tests should then be repeated periodically to monitor disease progression.

Differential Diagnosis

The early stages of DRESS may be difficult to distinguish from the much more commonly occurring, uncomplicated maculopapular drug eruption. The presence of facial edema, severe malaise, lymphadenopathy, and elevated transaminase levels is suggestive of DRESS.

The differential diagnosis for full-blown DRESS includes Kawasaki syndrome, secondary syphilis, and viral infections such as Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, and hepatitis B and C.

Therapy

The most important therapeutic measure in treating DRESS is to discontinue the causative medication. Construction of a drug calendar may be helpful. However, the list of drugs that cause DRESS is quite short, and identification of the causative agent is often much easier for DRESS than it is for other drug reactions. When two drugs are suspected, the offender is more likely to be the drug that was first taken for the first time during the preceding 2–6 weeks. Subsequent re-exposure to the causative medication can have catastrophic clinical consequences and should be avoided.

Therapy for DRESS is usually oral prednisolone given at 0.5–1.0 mg/kg/day. Some centers initially treat DRESS with intravenous hydrocortisone. Clinical features of DRESS may wax and wane for many months, and most patients receive a slow taper of their steroid therapy. Rapid tapering of steroid therapy may lead to severe flares in the hepatic disease, the skin disease, or the renal disease. In one series of 27 patients, the mean duration of systemic steroid therapy was 50 days (Ang et al. 2010).

Patients who have DRESS that is caused by one of the aromatic anticonvulsants (phenytoin, phenobarbital, or carbamazepine) may not be given another aromatic anticonvulsant owing to the high probability of cross-reaction. Some authors have suggested the use of a benzodiazepine or gabapentin for seizure control during the acute phase of DRESS (Vittrorio and Mugha 1995). Valproic acid is an alternative for seizure control, but it undergoes hepatic metabolism and should probably be avoided in the acute and early convalescent phases of DRESS. Lamotrigine is

another alternative for seizure control but is itself a potential cause of DRESS, so it is best avoided in this setting.

Acute Cutaneous GVHD

Hematopoietic stem cell transplantation (HSCT) is used to treat a variety of hematologic malignancies as well as selected solid tumors, immunodeficiency syndromes, and genetic diseases. More than 50,000 of these transplants are performed annually worldwide, and increasing numbers of them are allogeneic. Despite advances in preconditioning regimens and treatment, GVHD remains a significant cause of patient morbidity and mortality in patients who undergo HSCT. This section addresses some of the urgent problems associated with cutaneous GVHD.

Traditionally, cutaneous GVHD has been categorized as acute or chronic based on the timing of its appearance after HSCT; specifically, acute disease appears fewer than 100 days after engraftment, whereas chronic disease appears after more than 100 days. Development of both acute and chronic GVHD is now known to be not solely time-sensitive but also related to such factors as the type of transplant, the conditioning regimen, the number of T cells infused, and the degree of histocompatibility. In addition, tapering of immunosuppression, systemic infections, ultraviolet light exposure, or donor lymphocyte infusions (at any time after HSCT) may trigger GVHD flares. In 2005, the National Institutes of Health Consensus Development Project redefined acute and chronic GVHD to include subcategories based not only on the timing of symptoms after HSCT or donor lymphocyte infusion but also on the presence of acute and chronic GVHD features (Table 16.5). Therefore, emergency room providers should be aware that an acute eruption that occurs more than 100 days after HSCT may represent acute GVHD and thus be ready to intercede.

Table 16.5 Definitions of acute and chronic GVHD from the 2005 National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic GVHD

	Symptoms after HSCT or donor lymphocyte infusion	Presence of acute features	Presence of chronic features
Acute GVHD			
Classic acute	≤100 days	Yes	No
Persistent, recurrent, or late-onset acute	>100 days	Yes	No
Chronic GVHD			
Classic chronic	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

Based on data from Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 2005;11:945–56

Table 16.6 Consensus criteria for organ staging of acute GVHD

Stage	Skin	Liver	Intestinal tract
1	Erythematous macules and papules, <25 % of BSA	Bilirubin level, 2–3 mg/100 mL	Diarrhea, 500–1000 mL/day
2	Erythematous macules and papules, 25–50 % of BSA	Bilirubin level, 3–6 mg/100 mL	Diarrhea, 1000–1500 mL/day
3	Erythematous macules and papules (>50 % of BSA) to generalized erythroderma	Bilirubin level, 6–15 mg/100 mL	Diarrhea, 1500–2000 mL/day
4	Generalized erythroderma with bullae formation	Bilirubin level, >15 mg/100 mL	Diarrhea, >2000 mL/day; severe abdominal pain with or without ileus

Based on data from Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15:825–8

To quantify the degree of skin involvement by GVHD, researchers have formulated grading scales that take into account the percentage of BSA involved and the morphologic appearance of the eruption (Table 16.6).

Patients with early acute cutaneous GVHD sometimes complain of pruritus (or pain) in the palms, soles, or ears. The hands and feet become progressively edematous and purple, mimicking the changes of hand-foot syndrome (Fig. 16.5). The pain and swelling can be severe, prompting an emergency room visit for pain relief.

The most common presentation of acute cutaneous GVHD, however, is an erythematous maculopapular eruption that involves the trunk and proximal extremities. Early intervention, usually with systemic corticosteroids, may prevent progression of the eruption. When left unchecked, the rash may develop into an exfoliative erythroderma (i.e., stage III or IV acute cutaneous GVHD). Erythroderma is characterized by red scaly skin that involves more than 90 % of the BSA (Fig. 16.6). This inflamed red skin is no longer an effective environmental barrier, which increases the patient's risk of cutaneous infection and sepsis. Significant fluid shifts into the extracellular tissue may contribute to the development of hypotension, high-output heart failure, and peripheral edema. Affected patients have difficulty regulating body temperature and maintaining fluid and electrolyte balance and are hypermetabolic. They also complain of rigors and intractable itching or skin pain.

Patients with advanced acute cutaneous GVHD also may have blisters and denuded skin (Fig. 16.7). The blisters may be focal or widespread and are a result of epidermal necrosis. When extensive blisters are present, the clinical picture may be indistinguishable from the skin changes characteristic of TEN. The epidermal cells of the mucous membranes of the mouth and gastrointestinal tract also may be affected, causing severe mucositis. Furthermore, eye involvement may be severe. Recognizing signs of early epidermal necrosis before progression to full-thickness loss occurs is important. The loss of the epidermal barrier places these already immunocompromised patients at high risk for infection. Emergency intervention usually includes high-dose corticosteroids, sometimes in conjunction with other

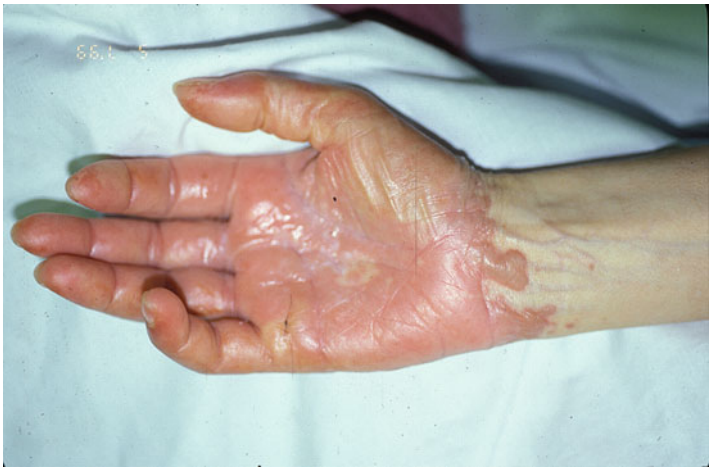

Fig. 16.5 Erythema, edema, and blisters of the hand in a patient with acute cutaneous GVHD

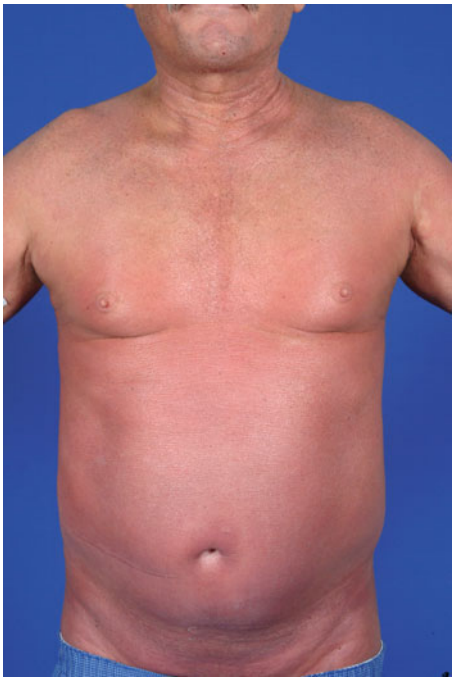

Fig. 16.6 Erythroderma in a patient with acute cutaneous GVHD

immunomodulatory medications. Skin biopsy may have a diagnostic role in these patients; however, the decision to intervene is often so urgent that it must be made before biopsy results are available. Topical care is directed toward the epidermal necrosis, and these patients are treated as if they had extensive second-degree burns or TEN.

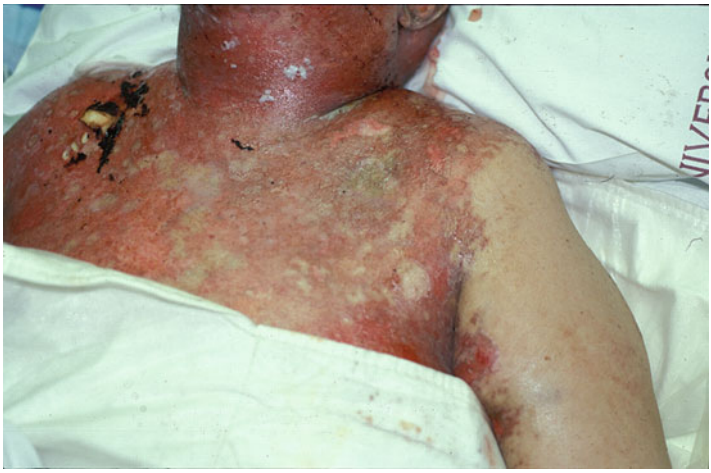

Fig. 16.7 Severe skin disease with blisters and erosions in a patient with acute cutaneous GVHD

A different and particularly lethal form of acute GVHD may occur in the absence of HSCT: transfusion GVHD, which occurs after a nonirradiated transfusion is given to a profoundly immunosuppressed host. Patients with transfusion GVHD present with a widespread rash, diarrhea, pancytopenia, and icterus and have a mortality rate exceeding 90 %.

Differential Diagnosis

The differential diagnosis for acute cutaneous GVHD includes TEN, DRESS, and conventional maculopapular drug exanthems. It also includes viral exanthems such as cytomegalovirus and Epstein-Barr virus. Distinguishing a drug-induced eruption from acute GVHD is sometimes difficult. Findings of diarrhea, dry mouth, and elevated transaminase levels may favor the diagnosis of GVHD.

Also in the differential diagnosis is the eruption of lymphocyte recovery. This is a maculopapular eruption that occurs 1–2 weeks after chemotherapy corresponding to the chemotherapy-induced hematologic nadir. Patients sometimes have transient fever that resolves in a few days. The histology of this disorder is nonspecific but may include epidermal changes with necrotic keratinocytes, similar to the histology of GVHD. Other systemic symptoms are usually not prominent features, but these patients are often urgently evaluated because of their fever and rash.

Engraftment syndrome is a true oncologic emergency with an explosive onset within 96 h after stem cell engraftment. Also called hyperacute GVHD, it may occur after both autologous and allogeneic HSCT independent of human leukocyte antigen disparity. The pathogenesis of this syndrome is likely a cytokine-driven capillary leak syndrome. Major diagnostic criteria include fever, noncardiogenic

pulmonary edema, and an erythematous rash involving more than 25 % of the BSA. Treatment with systemic corticosteroids produces a rapid improvement, but the disease may flare when the corticosteroids are tapered.

In summary, cutaneous GVHD is common after HSCT and has acute and chronic presentations. In some cases, especially when it is rapidly progressive, painful, or associated with compromise of cutaneous integrity, cutaneous GVHD is an oncologic emergency. Prompt recognition and early intervention may mitigate some of the severe complications of this disease.

Necrotizing Fasciitis

Necrotizing fasciitis is a devastating infection of the deep soft tissue and fascia. Host factors such as immunosuppression and malignancy play a significant role in predisposing patients to these infections. Patients receiving chemotherapy or biologic agents may be particularly at risk for necrotizing fasciitis; early recognition and multidisciplinary treatment are essential. Despite optimal surgical and antimicrobial treatment, necrotizing soft tissue infections are associated with a mortality rate approaching 25 %. Although many terms for this condition exist, the term necrotizing soft tissue infection is increasingly being adopted. Anatomically, necrotizing soft tissue infections may involve all soft tissue layers, including the dermis, subcutaneous tissue, superficial fascia, deep fascia, and muscle. Common pathologic features of these infections are extensive tissue destruction, spread of bacteria along fascial planes, and thrombosis of blood vessels. Although they are relatively uncommon in the United States, with an annual incidence of approximately 1000 cases, the lethal potential of necrotizing soft tissue infections warrants a high index of suspicion. Necrotizing soft tissue infections are surgical emergencies, and increasing time to intervention correlates directly with increasing mortality.

Epidemiology

Necrotizing soft tissue infections are classified into three main groups according to the types of bacteria involved (Table 16.7). Type I infections are polymicrobial and are the most common. They typically include infections with Gram-positive cocci, Gram-negative rods, and/or anaerobes. Type I infections tend to occur in the perineum or on the trunk of immunodeficient patients. Once common, *Clostridium* species are now rarely implicated in type I infections; they sometimes cause necrotizing infections that are associated with a perforated colon cancer or diverticulitis.

Type II infections are monomicrobial and are caused by a group A streptococcus (*Streptococcus pyogenes*) or by *Staphylococcus aureus*. These infections classically involve the extremities of the otherwise healthy immunocompetent host. Necrotizing

Table 16.7 Classification of necrotizing soft tissue infections

Type I	Polymicrobial Gram-positive cocci, Gram-negative rods, and anaerobes Location: perineum or trunk Patient population: immunocompromised
Type II	Monomicrobial Group A streptococcus: *S. pyogenes* *S. aureus*: consider methicillin-resistant *S. aureus* Location: extremities Patient population: healthy, immunocompetent
Type III	*V. vulnificus* Location: disrupted skin Patient population: those with liver failure

streptococcal infections are associated with toxic shock syndrome. Both *Streptococcus* and *Staphylococcus* species produce M proteins and exotoxins that prevent phagocytosis, damage endothelium, and ultimately cause cytokine release to produce a systemic inflammatory response. The incidence of community-acquired methicillin-resistant *S. aureus* infections is increasing.

Type III infections are caused by *Vibrio vulnificus*, a bacterium found in coastal areas. Patients with severe liver failure (especially owing to chronic hepatitis B) are vulnerable when disruptions in the skin are exposed to warm sea water. *V. vulnificus* produces exotoxins capable of initiating cardiovascular collapse before skin changes are evident.

Patients at risk for necrotizing soft tissue infections include intravenous drug users and those with chronic illnesses, including diabetes, obesity, immunosuppression, chronic kidney disease, and malignancies. A retrospective review by Childers and colleagues demonstrated that malignancy, renal disease, and congestive heart failure markedly increase mortality rates in patients with necrotizing fasciitis (Childers et al. 2002). However, the precipitating event for necrotizing soft tissue infection is unknown in more than 20 % of cases.

Presentation and Diagnosis

Initial signs of erythema, tenderness, and edema beyond the area of infection are frequently seen in patients with necrotizing soft tissue infections. As with all ischemic processes, pain may be out of proportion to physical examination findings. Systemic findings of fever and tachycardia may be absent in the immunocompromised cancer patient. As the infection progresses, ecchymoses, blisters, crepitus, and tense edema develop beyond the immediate area of infection (Fig. 16.8). In such cases, the general surgical service must be consulted on an emergency basis. Hemorrhagic bullae form as blood vessels thrombose. Crepitus of the skin is present in only 13–31 % of patients. Cardiovascular collapse prior to skin changes is caused

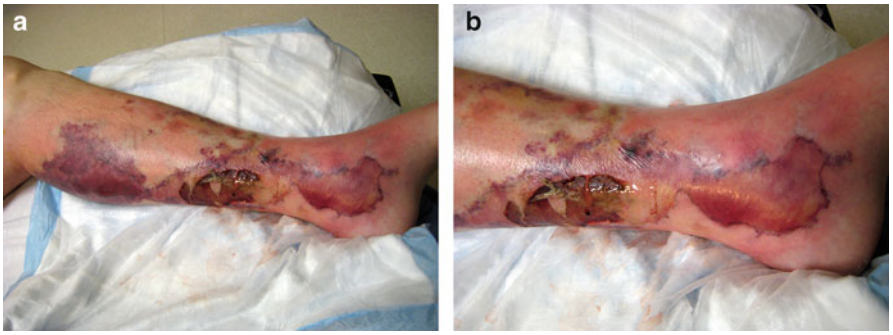

Fig. 16.8 (**a**) Ulceration and ecchymoses in a patient with necrotizing fasciitis. (**b**) Close-up of the patient's ulceration and ecchymoses

Table 16.8 Laboratory risk indicator for necrotizing fasciitis scoring system

Value	LRINEC score
C-reactive protein level, mg/L	
<150	0
>150	4
White blood cell count, cells/mm^3	
<15	0
15–25	1
>25	2
Hemoglobin level, g/dL	
>13.5	0
11–13.5	1
<11	2
Sodium level, mmol/L	
>135	0
<135	2
Creatinine level, mg/dL	
<1.6	0
>1.6	2
Glucose level, mg/dL	
<180	0
>180	1
Total	0–15

Based on data from Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: A tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med. 2004; 32:1535–41

by endogenous cytokine release and bacteria-derived toxins. A necrotizing soft tissue infection should be suspected in any patient presenting with fever, sepsis, and stigmata of soft tissue infection with disproportionate pain.

The differential diagnosis for necrotizing soft tissue infections includes pyoderma gangrenosum.

Researchers have developed many scoring systems to expedite the diagnosis of necrotizing soft tissue infections. Whereas none of these systems supplant sound clinical judgment, the Laboratory Risk Indicator for Necrotizing Fasciitis score (Table 16.8) can help stratify patients into risk categories. This tool applies scores to derangements in six common laboratory parameters: white blood cell count and C-reactive protein, hemoglobin, sodium, creatinine, and glucose level. Scores range from 0 to 15. Most patients with necrotizing soft tissue infections have scores higher than 6. The probability of disease increases proportionately as the score increases; a score greater than 7 has a 75 % positive predictive value.

Although sometimes helpful, radiologic studies cannot be used to exclude necrotizing soft tissue infections because of inherently high false-negative rates; a lack of radiologic findings should not delay operative treatment. Plain films demonstrating subcutaneous emphysema are diagnostic, but this finding occurs in a minority of patients. Computed tomography, which is rapid and widely available, has improved diagnostic sensitivity by demonstrating inflammatory changes. Magnetic resonance imaging is rarely used because it may delay diagnosis and tends to overestimate deep tissue involvement. Ultrasound lacks sensitivity and specificity and does not have a role in the diagnosis of necrotizing soft tissue infections.

Treatment

The essential elements of treatment of necrotizing soft tissue infections are surgical exploration and wide debridement, antimicrobial therapy, and supportive care. Early and aggressive surgery influences survival. Wong and colleagues reported a ninefold increase in mortality rate when surgery was delayed more than 24 h (Wong et al. 2003). For this reason, early excision of the necrotic tissue, even without a confirmed diagnosis, is justified. Excision should include all cellulitic skin and necrotic tissue with the goal of attaining healthy, bleeding tissue margins. Mok et al. (2006) noted a 7.5-fold increase in relative risk of death when debridement was incomplete. Upon surgical exploration, findings consistent with necrotizing soft tissue infections include gray necrotic tissue that does not bleed, thrombosis of small vessels, “dishwater” pus, noncontracting muscle, and lack of resistance to finger dissection along normally adherent planes. Amputation is considered when the infection involves a joint or spreads rapidly toward the torso despite attempts at surgical control or when the extent of muscle necrosis would render an extremity functionless. Analysis of frozen sections is rarely beneficial owing to difficulties in interpretation. However, Gram staining and culture of the pus may guide subsequent antimicrobial therapy.

In the setting of a very extensive infection, serial debridement at 6- to 48-h intervals should be performed until no further necrosis or infected tissue is visible.

A decline in the patients' status or an increasing white blood cell count should prompt earlier re-exploration of the wound. In the case of perineal infection, a diverting colostomy is considered to facilitate wound management. Initially, wet to dry dressings are preferred, although hydrogel dressings may be used. Once the infection is controlled, use of a wound vacuum device may enhance granulation and improve time to wound closure.

Use of broad-spectrum antimicrobials is an adjuvant to surgery and should be initiated early. Initial coverage should target Gram-positive, Gram-negative, and anaerobic bacteria. Many antimicrobial regimens have been advocated, including monotherapy with imipenem, meropenem, ertapenem, piperacillin/tazobactam, or tigecycline. The classic multidrug therapy includes high-dose penicillin, clindamycin, and either a fluoroquinolone or an aminoglycoside. In the current era, in which methicillin resistance is common, treatment of necrotizing soft tissue infections should include vancomycin, linezolid, or daptomycin until methicillin-resistant staphylococcal infection is excluded. The use of clindamycin remains important because this agent inhibits M protein and exotoxin synthesis in patients with group A streptococcal infections. Tetracycline and third-generation cephalosporins appear to reduce mortality rates in patients with *V. vulnificus* infections. The spectra of the antibiotic regimens can be narrowed with tissue and blood culture data. Antibiotic treatment should be continued until surgical debridement is complete and the systemic inflammatory process has resolved.

Hyperbaric oxygen and IVIG-based therapies for necrotizing soft tissue infections are controversial. Owing to a lack of data supporting these novel treatments, they are currently reserved for patients with severe infection and high mortality risk who have already received optimal surgical management. The proposed benefit of hyperbaric oxygen therapy is that increased oxygen delivery inhibits anaerobes, decreases exotoxin production, improves leukocyte function, and enhances antibiotic effects. Also, particularly in patients with staphylococcal or streptococcal infections, IVIG decreases the systemic inflammatory response by binding exotoxins.

Key Practice Points

- Stevens-Johnson syndrome and staphylococcal scalded skin syndrome are included in the differential diagnosis for the febrile patient who has tender skin and widespread blisters. The presence of mucosal involvement is suggestive of SJS. Skin biopsy for frozen section analysis may rapidly differentiate between these two disorders.
- In the acutely ill patient with a maculopapular eruption and hepatitis, consider the possibility of drug reaction with systemic symptoms. Medications that cause this severe drug reaction include phenytoin, trimethoprim-sulfamethoxazole, and minocycline.
- The onset of acute GVHD may be delayed in hematopoietic stem cell transplant recipients and sometimes occurs more than 100 days after transplantation. Gastroenteritis and hepatitis are common. Some patients have severe skin dis-

ease with erythroderma and blisters. Early therapeutic intervention is important to halt disease progression.

- Necrotizing fasciitis occurs more frequently in the immunosuppressed patient. Erythema and edema beyond the primary site of infection often occur. Pain may be out of proportion to physical examination findings. Fever and tachycardia, although common, may be absent in the immunosuppressed cancer patient with necrotizing fasciitis. Therapy consists of urgent debridement and the use of broad-spectrum antimicrobials.

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Chapter 17
Ophthalmologic Emergencies

Stella K. Kim

Contents

Chapter Overview

True ocular emergencies are ocular chemical burn and acute angle-closure glaucoma, both of which lead to blindness in seconds to minutes without intervention. These two conditions are not commonly seen in the emergency centers of cancer hospitals and are no more common in cancer patients than in the general population. Ocular emergencies in cancer patients are typically related to infections given the obvious immune status of this population. Ocular surface disease, which is typically

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not an emergency and is common owing to cancer treatments such as chemotherapy, irradiation, and stem cell transplantation, can lead to ocular emergencies, such as corneal perforation. However, symptoms alone do not often reflect the severity of serious ocular conditions. The spectrum of ocular symptoms reported by cancer patients may include ocular irritation, photophobia, redness, discharge, eye pain, double vision, and the most innocuous symptom of blurred vision. Each of these symptoms may represent relatively benign ocular disorders, ranging from cancer treatment-related dry eyes, which can be successfully treated with topical lubrication, to visually disabling ocular and orbital infections, which may lead to irreversible vision loss. This chapter describes the spectrum of ocular emergencies in patients at The University of Texas MD Anderson Cancer Center.

Introduction

Ocular pathology affecting cancer patients is organized in this chapter in an anatomical fashion, from the front of the eye to the back. In general, serious vascular and infectious problems can occur in our patient population given their immuocompromised and abnormal hematologic status. Ocular symptoms alone do not often suggest the serious nature of ocular pathology. Prompt ophthalmologic consultation is important in the treatment and long-term management of ocular disorders in cancer patients.

Orbital Cellulitis

Orbital cellulitis is an ophthalmologic emergency that requires prompt evaluation and treatment. Presentation typically occurs in the setting of sinusitis, a common condition in the cancer population (Bullock 1986). Signs and symptoms include tearing, eye pain, blurred vision, and periocular edema/erythema. Patients with preseptal cellulitis, which is cellulitis of the eyelid and/or skin around the eye, may have the same presentation. Even with preseptal cellulitis, eyelid swelling can be impressive, and patients may not be able to open the affected eye. Furthermore, in neutropenic cancer patients, the evaluation and initial treatment of preseptal and orbital cellulitis may be identical.

Signs of orbital cellulitis include proptosis, restrictive ophthalmoplegia (resulting in true double vision that patients may describe as blurred vision), and pupillary response abnormality (reflecting optic nerve dysfunction and decreased vision) in addition to the signs and symptoms of preseptal cellulits (Fig. 17.1). Ocular evaluation should include measurement of the degree of proptosis, limitation of motility, formal visual field testing if possible (confrontation visual field examination in the emergency room), pupillary response and color vision testing (reflecting optic nerve

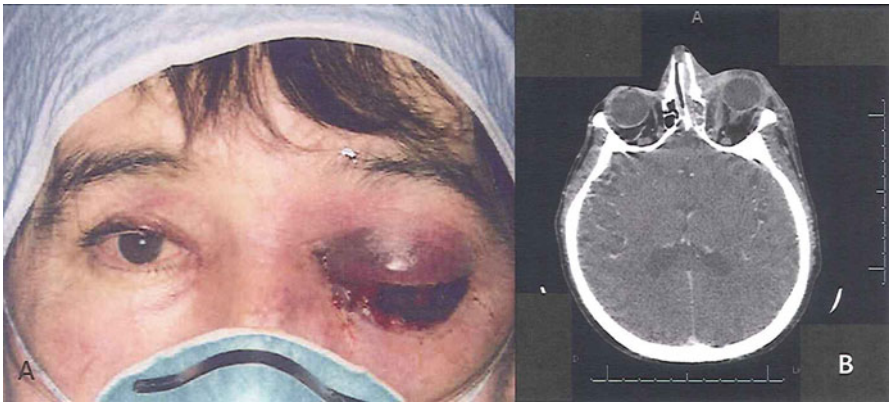

Fig. 17.1 (**a**) Hemorrhagic orbital cellulitis in a patient with neutropenic fever, thrombocytopenia with proptosis, ophthalmoplegia. and optic nerve dysfunction. (**b**) Computed tomography scan showing ethmoid sinusitis with strands in the soft tissue in the orbit and an obvious proptosis

function), and a dilated examination with attention to the optic nerve appearance. Orbital computed tomography is required to rule out sinusitis, which is typically the cause of orbital cellulitis. Other radiologic findings include orbital fat infiltration ("dirty fat") and stretching of the optic nerve (Fig. 17.1) (Howells and Ramadan 2001; Rudloe et al. 2010). If sinusitis is present, urgent head and neck surgery consultation is crucial to check for the presence of eschar formation on the nasal turbinates (to rule out mucormycosis) and prepare the patient for possible surgical debridement (Schell et al. 2008).

Cancer patients with orbital cellulitis, especially those with sinusitis, are admitted for broad-spectrum antimicrobial coverage with close monitoring of the infection. If surgery is deemed necessary for sinusitis owing to its extent or impact on the ocular structures, urgent surgical debridement is performed, after which intravenous antimicrobial treatment may be used depending on culture findings and sensitivity resulting from the debridement. Commonly involved organisms are those typically found in the nasal passages: *Staphylococcus* and *Streptococcus* species followed by *Haemophilus influenzae*, *Klebsiella pneumoniae*, and fungi (Schell et al. 2008; Chaudhry et al. 2008; Epstein and Kern 2008; Durand 2008). The infectious disease service should be involved in guiding the treatment regimen, particularly for patients who are severely immunocompromised during chemotherapy or immunosuppressed after allogeneic transplantation.

If the sinusitis is not controlled and leads to worsening ocular symptoms, repeated debridement may be necessary. Frequent ophthalmologic evaluations are important in monitoring optic nerve function (vision check, visual field, pupillary response, and color tests), eye motility, and proptosis level. Once the condition appears to stabilize, follow-up may be decreased until the patient can be discharged. The optimal approach to management of orbital cellulitis, especially in patients with acute or chronic sinusitis, is for the primary team to work in a multidisciplinary

fashion with the ophthalmology (oculoplastics in particular), infectious disease, and head and neck surgery services (Schell et al. 2008; Durand 2008).

Corneal Ulceration and Perforation

Corneal ulcers in patients with infections or nonhealing corneal wounds can lead to corneal thinning and perforation, which is an ocular emergency. The cornea is composed of highly innervated avascular tissue that is approximately 0.5 mm thick with unique, complex wound-healing properties. When the corneal epithelium does not heal, the corneal stroma can continue to thin, leading to perforation. Chemotherapy, allogeneic transplantation, irradiation of the ocular region, and surgery that distorts the eyelid and/or orbit position can have many side effects on the ocular surface and/or cornea, such as chronic dryness, inflammation, corneal thinning, exposure keratopathy (the eyelids do not close completely), and neurotrophic keratopathy (corneal sensation is diminished, predisposing the cornea to decreased wound-healing capacity and infections). These conditions can predispose the cornea to microabrasions or large epithelial defects where infection ulcers can occur; given the immune status of cancer patients, such infections are often severe. Irradiated eyes are particularly susceptible to ocular surface diseases and infections (Chaques et al. 2000; Yoshida et al. 2006). Often, these patients also have globe and eylid position malformation, particularly patients with head and neck cancer requiring surgery followed by chemoradiation, which increases the patient's risk of ocular infections (Fig. 17.2).

Patients with corneal ulceration may experience redness, discharge, blurred vision, and the appearance of opacity on the cornea, often without pain in a neurotrophic cornea (Fig. 17.3). Patients using contact lenses harbor worse microbial

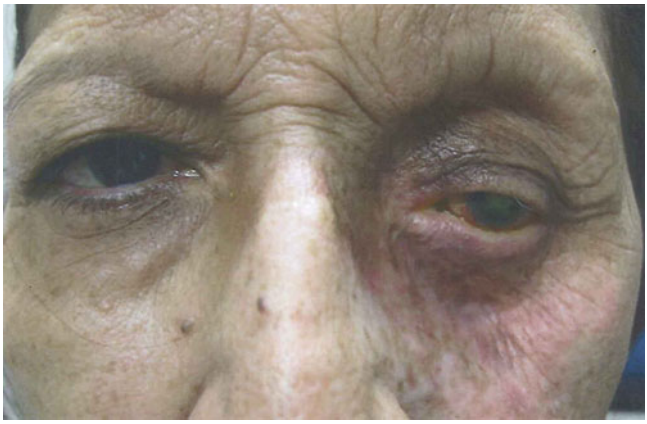

Fig. 17.2 Status of a patient with hypoglobus, enophthalmos, and exposure and neurotrophic keratopathy with a corneal ulceration after maxillectomy and radiotherapy

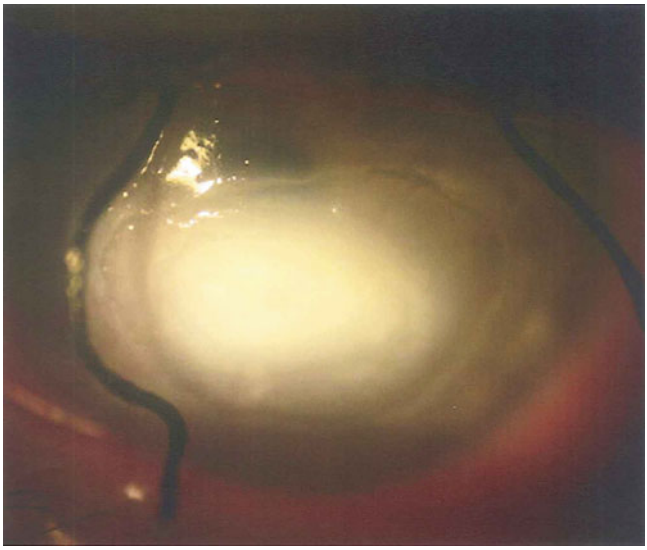

Fig. 17.3 A corneal ulcer with dense white infiltration and corneal thinning. Sutures on the lids are for opened temporary tarsorrhaphy performed to protect and promote a neurotrophic cornea

flora and experience worse corneal infections than do patients who do not wear them. This is an important consideration for cancer patients, who should avoid wearing contact lenses during their treatment, as the lenses can serve as sources of severe corneal ulceration. Workup for a moderately sized corneal ulcer includes gently scraping the cornea for Gram staining and culture. A wide spectrum of microbes (bacterial, fungal, and, less likely, viral) can infect the cornea, but the typical infecting organism is either Gram-positive or -negative (Durand 2008). Treatment with fortified topical broad-spectrum antibiotic drops is performed around the clock along with frequent lubrication. Topical antifungal treatment is usually started only when the index of suspicion for infection is high (according to the pattern of infection on the cornea, a Gram-positive stain, or a positive fungal culture after cornea scraping, which can take up to several weeks) (Schell et al. 2008). Typically, patients receive therapy in an outpatient setting and are observed daily until their condition improves. For a nonhealing corneal ulcer with persistent epithelial defects, especially in a patient with a neurotrophic cornea, surgical intervention, such as temporary tarsorrhaphy and an amniotic membrane patch graft, may be required to promote epithelial healing. If the cornea continues to thin despite these measures, corneal perforation may occur (Fig. 17.4).

Perforation of the cornea is a serious ocular emergency, as it is an opened globe, requiring immediate closure. Patients with corneal perforation are admitted to the hospital for intravenous administration of antibiotics to prevent endophthalmitis (an infection inside the eye) and should undergo surgery as soon as possible. The primary goal of treatment is to re-establish the integrity of the eye by closing the open wound via any measure necessary, with visual rehabilitation being the secondary

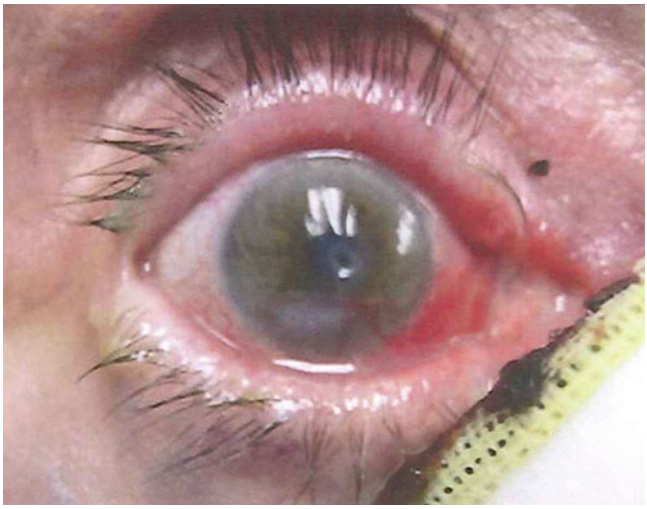

Fig. 17.4 Eye of a patient with abnormal eyelid closure and a neurotrophic cornea after maxillectomy. Of note is the central hole in the cornea (corneal perforation) with corneal scarring inferiorly from the area of chronic exposure keratopathy

goal. The surgical approach depends on the location and degree of the perforation. Unlike the conjunctiva, the cornea cannot be closed with sutures alone when tissue loss such as ulceration or corneal melt occurs. Microperforations can be managed urgently in the clinic with cyanoacrylate glue and a bandage contact lens (Fig. 17.5) in preparation for surgical repair, which may include a multilayer amniotic membrane with a patch graft if the perforation is small. For larger corneal perforations, urgent penetrating corneal transplantation may be needed (Schell et al. 2008; Durand 2008; Azuara-Blanco et al. 1999).

Acute Graft-Versus-Host Disease (Stage IV)

Graft-versus-host disease (GVHD) can occur in a patient who undergoes allogeneic stem cell transplantation (SCT) when the graft, in this case, the donor cells (peripheral blood stem cells or bone marrow cells obtained from either a related or unrelated matched donor or stem cells obtained from cord blood), react to the patient (the host). GVDH is one of the greatest impediments to successful SCT (Wolf et al. 2012). Acute GVHD typically occurs early after SCT (no more than 100 days) and can affect the skin, liver, gastrointestinal tract (including the mouth), lungs, and eyes. Grade IV GVHD is a severe form of acute systemic GVHD involving multiple organs in which the patient may experience significant bullar formation, skin desquamation, liver abnormalities, and gastrointestinal dysfunction. Patients with acute GVHD are admitted as inpatients and given multiple modalities of

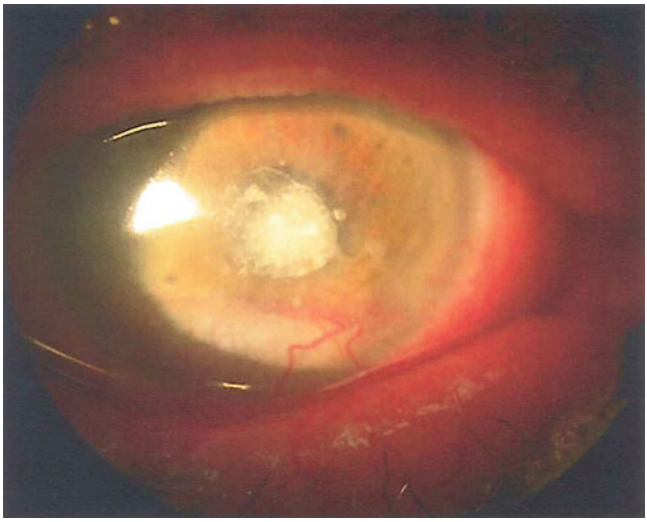

Fig. 17.5 Use of cyanoacrylate glue for closure of a corneal perforation covered with a bandage contact lens

immunosuppressive therapy. Acute stage IV ocular GVDH can occur as an ophthalmologic emergency in this setting (Kim et al. 2008).

Stage IV ocular GVHD is a rare form of GVHD in which the bilateral corneal epithelium can slough completely off in a patient with intense conjunctival inflammation having pseudomembranous and membranous keratoconjunctivitis, lacrimal gland dysfunction, and ulcerations (Fig. 17.6). The sloughing of corneal epithelium requires evaluation and treatment, as an exposed cornea with a large epithelial defect can result in corneal thinning, infection, ulceration, and perforation (Jabs et al. 1989). Patients with stage IV ocular GVHD experience intense eye pain, as the cornea is the most sensitive part of the body with the highest density of sensory nerve fibers, as well as discharge, debilitating photophobia, and blurred vision. In addition, patients typically are unable to fully open their eyes owing to their discomfort. Often, patients with stage IV ocular GVHD must be examined at the bedside because their condition does not allow for transfer from a hospital room to the clinic for evaluation. Stage III ocular GVHD (pseudomembranous/membranous conjunctivitis without corneal epithelial sloughing) also requires aggressive treatment to prevent both progression to stage IV disease and scarring of the palpebral conjunctiva. Stage III ocular GVHD is not as severe as stage IV disease because the corneal epithelium remains intact.

Examination of acute ocular GVHD is typically difficult owing to its severity, and topical anesthetic drops are used to aid in the evaluation. Workup should include a viral swab and/or culture to rule out a concomitant viral infection, which can have a presentation similar to that of GVHD. Optimal treatment of systemic GVHD is required. However, once it becomes steroid-refractory, acute GVHD is challenging

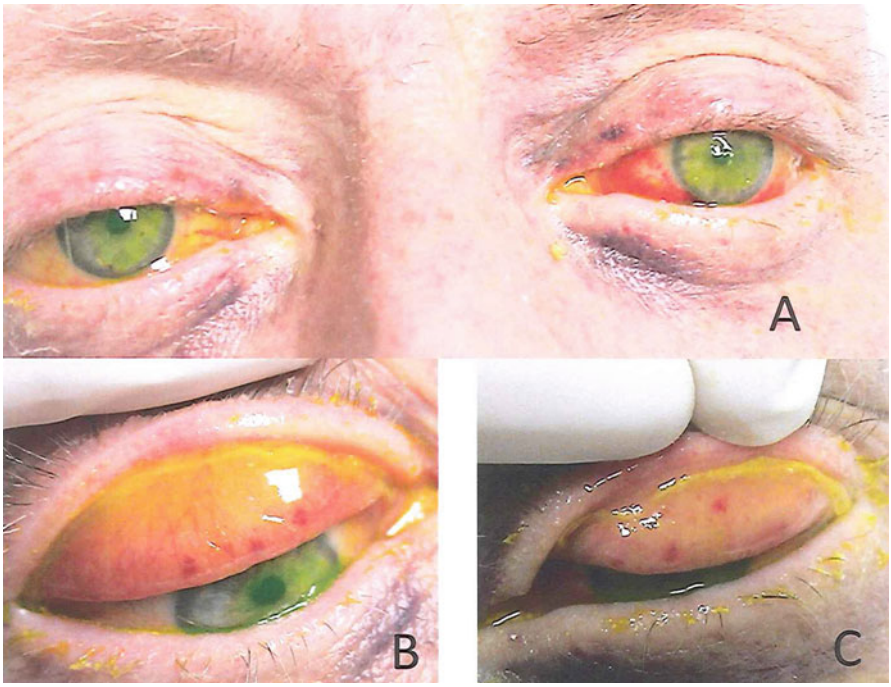

Fig. 17.6 (**a**) Stage IV ocular GVHD in a patient with stage IV systemic GVHD after SCT. (**b** and **c**) Everted upper eyelids exhibiting pseudomembranous/membranous keratoconjunctivitis requiring debridement. The *yellow coloration* is the fluorescein uptake of denuded corneal epithelium

to manage, requiring the use of a variety of immunomodulating agents and photopheresis. Furthermore, management of ocular GVHD is equally challenging for both the patient, who is very ill, and the physician, who may have to perform ocular procedures at the bedside (Kim et al. 2008).

At MD Anderson, stage IV ocular GVHD is treated with debridement of the necrotic ocular tissue (pseudomembranes/membranes on the palpebral conjunctiva) (Fig. 17.7) with or without amniotic membranes (which can be achieved via insertion of a commercially available amniotic membrane ring device). Hourly application of a topical steroid is often needed in addition to that of topical prophylactic antibiotics and copious lubrication. Punctal occlusion with silicone plugs is important in not only addressing a lack of tearing but also increasing the topical medication on the ocular surface by prohibiting its drainage into the nasolacrimal duct. Patients must be monitored closely for recurrence of pseudomembrane and/or membrane formation, which can often necessitate repeated debridement, and for re-epithelization of the cornea. The prognosis for stage IV ocular GVHD can be surprisingly encouraging if treated expeditiously, although the visual outcome depends on the rate at which the cornea heals. The danger of a persistent corneal epithelial defect is its accompanying risk of perforation, which may lead to endophthalmitis, loss of vision, or loss of the eye, all of which underscores

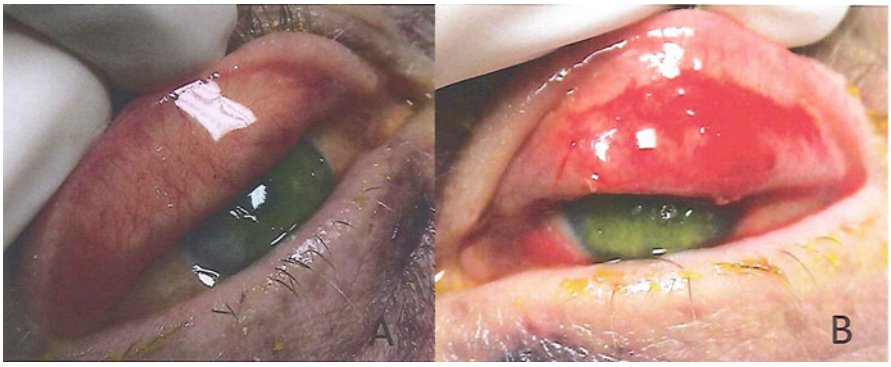

Fig. 17.7 Postsurgical debridement of the (**a**) right upper eyelid and (**b**) left upper eyelid for treatment of stage IV ocular GVHD

the importance of close follow-up for patients with stage IV ocular GVHD. The prognosis for stage IV systemic GVHD is related to whether it responds to the use of systemic steroids, and it can be guarded for patients whose disease is refractory to steroids (Kim et al. 2008).

Herpetic Disease

Herpes reactivation is common in cancer patients. Patients often undergo prophylaxis with antiviral medications (either acyclovir or valacyclovir) during their cancer treatment. Herpes zoster infection can involve the eye with V1 distribution of the trigeminal branch (herpes zoster ophthalmicus) (Fig. 17.8), whereas herpes simplex virus infection can present as patient-described conjunctivitis. An ophthalmologic

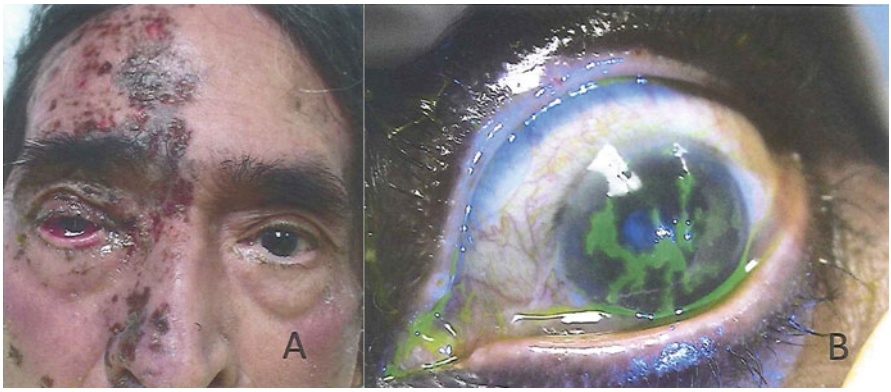

Fig. 17.8 (**a**) V1 distribution of herpes zoster virus infection (herpes zoster ophthalmicus). (**b**) Classic corneal dendritic keratitis caused by herpes simplex virus

consultation is performed when a patient presents with herpes zoster ophthalmicus, has vesicles characteristic of herpes simplex virus infection around the eye and/or eyelids, or has disseminated herpes (Johnson 2008).

Symptoms of herpetic disease range from ocular irritation and epiphora to severe pain, photophobia, discharge, redness, and blurred vision. Both herpes simplex virus and herpes zoster infection can cause classic dendritic keratitis, which affects the corneal epithelium (Fig. 17.8). They may also cause conjunctival inflammation, significant scarring and cicatricial conjunctivitis, corneal stromal keratitis, iritis, uveitis, and trabeculitis (inflammatory glaucoma) (Johnson 2008; Kaufman 2008; Knickelbein et al. 2009). Development of a herpetic infection involving the retina is an ophthalmologic emergency. Although rare, herpetic retinitis can lead to irreversible vision loss and other intraocular complications in cancer patients.

Ophthalmologists typically refer to retinitis caused by herpes simplex as acute retinal necrosis and by herpes zoster as peripheral outer retinal necrosis, but the processes are basically similar in that the infections result in retinal necrosis, which often leads to friable tissue with retinal holes and detachment (Fig. 17.9). The appearance of herpetic retinitis is similar to that of viral retinitis regarding whiten-

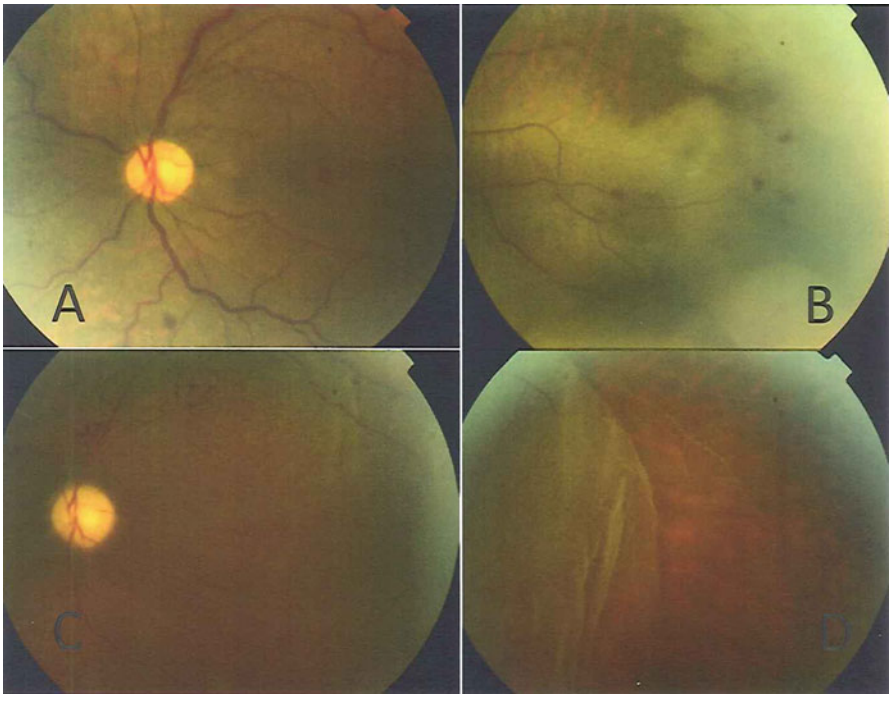

Fig. 17.9 (**a**) Acute retinal necrosis. (**b**) The retina appears white (necrotic) mixed with occasional retinal hemorrhage. (**c**) The optic nerve appears pale, with a thinned retina and sclerotic ghost vessels. (**d**) Giant retinal detachment in the periphery from the thinned retina

ing of the retina, but it may not result in as much retinal hemorrhage as that associated with cytomegalovirus (CMV) retinitis. Examination of a vitreous specimen obtained via a tap for polymerase chain reaction analysis (which can be done at the bedside, if needed) can aid in diagnosis. Also, spinal fluid may be evaluated for the presence of infection depending on the clinical scenario, but if this cannot be done because the patient has a low platelet count or is deferred for other medical considerations, foscarnet is administered intravenously for improved central nervous system penetration (Johnson 2008; Holland 1994; Guex-Crosier et al. 1997; Davis et al. 2008).

Treatment of herpetic disease depends on the immune status of the patient, but typically, patients are given intravenous antiviral medications with infectious disease specialist input as well as topical ocular medications in the hospital if the cornea is involved. Such medications include topical trifluridine (up to 9 times a day) or ganciclovir ointment, topical antibiotic drops or ointment, a topical steroid if the patient has significant anterior uveitis, and, if needed, an antiglaucoma medication. Corneal or conjunctivital debridement may be necessary if the patient has a large area of dendritic keratitis or pseudomembranous conjunctivitis and/or cicatricial conjunctivitis with significant symblepharon (scar tissue on the conjunctiva) (Johnson 2008; Knickelbein et al. 2009; Davis et al. 2008; Kaufman and Haw 2012).

If retinitis is present, management of herpetic disease is challenging, and visual recovery is less likely than in patients without retinitis. Intravitreal injection of acyclovir or ganciclovir in addition to systemic antiviral therapy can help control rapidly expanding retinitis (Johnson 2008; Davis et al. 2008; Yin et al. 2007). Intravitreal injection of antimicrobial medications, particularly antibiotics, is considered the standard of care for infectious endophthalmitis, although intravitreal injection is an off-label use of antibiotics. Even if the infection is controlled, damage to the retina results in thinned friable tissue that is predisposed to holes and detachments, which are difficult to treat surgically. Unlike acute retinal necrosis in immunocompetent patients, acute retinal necrosis and peripheral outer retinal necrosis in immunocompromised cancer patients are often rapidly progressive and result in poor visual outcome. Aggressive antiviral therapy is required for herpetic retinitis (Johnson 2008; Davis et al. 2008).

CMV Retinitis

Similar to herpes, CMV reactivation is common in immunocompromised cancer patients. Patients undergoing allogeneic SCT are routinely checked for CMV antigenemia in some centers, and patients positive for it undergo prophylaxis. Human immunodeficiency virus-infected individuals are routinely checked for CMV retinitis, but with the advent of triple therapy for acquired immunodeficiency syndrome, the incidence of CMV retinitis in this population has decreased. It is now more common in cancer patients, particularly after allogeneic transplantation

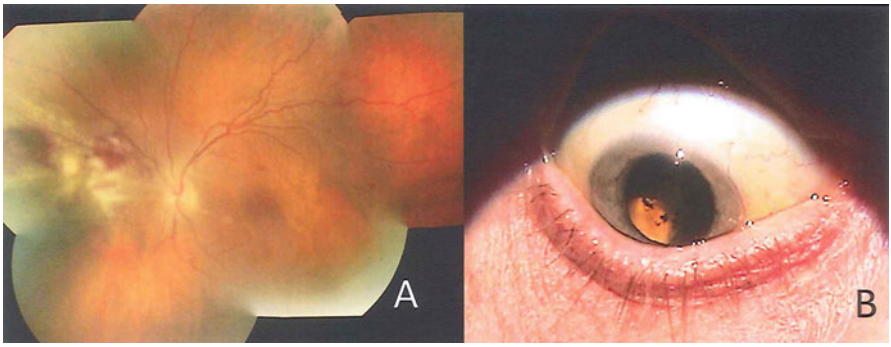

Fig. 17.10 (**a**) CMV retinitis. (**b**) Transillumination of a gancyclovir implant in the inferotemporal region of the posterior chamber (not the same patient as in **a**)

(Johnson 2008; Jeon et al. 2012; Tarver-Carr and Dunn 2008; Butler and Thorne 2012).

Symptoms of CMV retinitis can be innocuous ones such as blurry vision, but often, patients may not have any symptoms, pain, or even appearance of conjunctivitis. Routine examination, particularly of patients positive for CMV antigenemia, may identify CMV retinitis (Fig. 17.10). Upon examination, a patient with CMV retinitis has a white necrotic retina with patchy retinal hemorrhages that, if involving a large area, is described as having a "pizza-pie" appearance (Johnson 2008; Tarver-Carr and Dunn 2008).

Patients with CMV retinitis are typically admitted to the hospital for intravenous antiviral treatment, particularly immunodeficient patients undergoing cancer treatment, and observed on a daily basis for stability or improvement. Retinitis can progress quickly, and when it threatens the retinal region, it may permanently damage central vision, leading to blindness. Infectious disease consultation is often necessary to optimize the antiviral therapy while avoiding compromise of the patient's overall myelosuppression or renal function (Johnson 2008).

Intravitreal injection of ganciclovir can be used as an adjuvant to systemic treatment of CMV retinitis. This is an off-label use of ganciclovir similar to that of intravitreal injection of all antimicrobial medications (Tarver-Carr and Dunn 2008; Hoffman and Skiest 2000). Intravitreal injection is performed with topical anesthetic drops either at the bedside or in the clinic and typically by retina specialists, and it can be repeated frequently without serious toxicity. It may be required for CMV retinitis that threatens the macula and/or when systemic antiviral treatment does not adequately control progression of the retinitis. For long-term control of CMV retinitis, particularly when the patient's renal status is poor or the patient is myelosuppressed because of long-term antiviral therapy, surgical insertion of an intravitreal ganciclovir implant should be considered (Fig. 17.10) (Tarver-Carr and Dunn 2008). Visual recovery depends on the area of the retina affected by the infection, as visual function typically does not return in an area of retinal necrosis (Johnson 2008; Tarver-Carr and Dunn 2008).

Endogenous Endophthalmitis

Endophthalmitis is intraocular inflammation of the entire globe. It is typically caused by an infection, although inflammatory or infiltrative processes can cause it, as well. Most cases of endophthalmitis occur in the setting of postintraocular surgery or other procedures and trauma. In cancer patients, infectious endophthalmitis is typically caused by an endogenous systemic infection. Endophthalmitis must be addressed in an emergent fashion with proper treatment to preserve vision and the eye (Schell et al. 2008; Durand 2008).

Symptoms of endogenous endophthalmitis range from intense eye pain, blurred vision, redness, and eyelid and conjunctival swelling to very mild photophobia and blurred vision. Cancer patients admitted to the hospital for neutropenic fever with bacteremia or fungemia typically undergo ophthalmologic evaluation to rule out ocular involvement. Usually, they do not have any ocular findings. When ocular examination reveals a suspicious "white lesion" in the retina without evidence of vitritis or other clinical findings, whether the lesion is a single area of an infectious embolus or an area of either resolving hemorrhage or ischemia is often unclear given the patient's low hemoglobin or platelet count. Serial dilated examinations may be the only required treatment to ensure resolution of endogenous endophthalmitis, as both an ischemic retina and hemorrhage will resolve with time (Schell et al. 2008; Durand 2008).

Signs of endogenous endophthalmitis vary and include infectious emboli in the retina with mild vitritis and anterior chamber reactions causing minimal decreases in vision. A severe sign is that of a "hot" eye with profound loss of vision and frank hypopyon in the anterior chamber accompanied by acute conjunctival inflammation and corneal edema, dense vitritis, and chorioretinal infiltrations (Fig. 17.11). The view into the eye may be limited, in which case ultrasonography must be performed to evaluate the integrity of the globe. Patients with endogenous endophthalmitis are typically inpatients, but on rare occasions, they present to the emergency room or

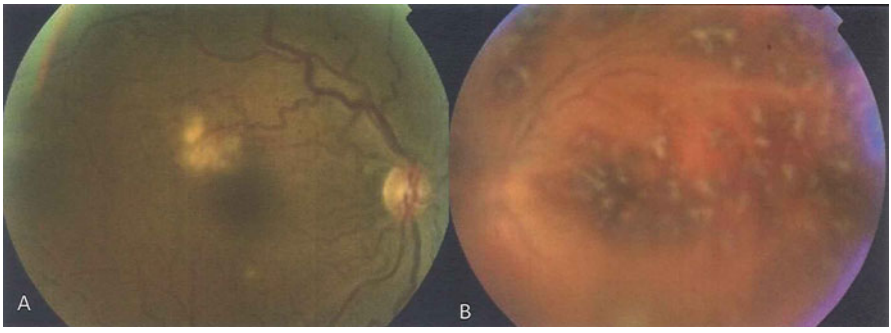

Fig. 17.11 (**a**) Endogenous endophthalmitis owing to fungal infiltration. (**b**) Endogenous bacterial endophthalmitis owing to endocarditis. The hazy view is caused by vitritis

ophthalmology clinic with eye-specific problems as the manifestations of their systemic infections (Durand 2008).

Treatment of endogenous endophthalmitis consists of intravenous broad-spectrum antimicrobials along with intravitreal injection of antibiotics (usually vancomycin and tobramycin, possibly antifungal and antiviral medications). If the patient's blood culture is positive for infection or Gram staining of a specimen obtained via a vitreous tap is informative, the intravitreal injections can be tailored to the infecting organism (Schell et al. 2008; Durand 2008). Patients with endophthalmitis and without a recent history of trauma or ocular surgery must undergo workup to identify the source of the systemic infection, which should include blood cultures, echocardiography to rule out endocarditis, a chest X-ray, an intravenous line/indwelling catheter culture, and, depending on the clinical scenario, neuroimaging and spinal tap analysis. Although it varies with the type of organism, visual prognosis for endogenous endophthalmitis is guarded. As is the case for retinitis and all other entities described in this chapter, urgent evaluation, diagnosis, and treatment are crucial to ensuring the optimal outcome of endophthalmitis (Schell et al. 2008; Durand 2008; Johnson 2008).

Cranial Palsies, Optic Neuropathy, and Papilledema

Optic nerve problems and other cranial nerve palsies typically require urgent ophthalmologic evaluation. Patients often describe blurred vision owing to refractive error (correctable with glasses) as double vision, whereas patients with cranial nerve palsies and true diplopia may describe their symptoms as blurred vision. Even in patients experiencing true diplopia, ocular deviations may be subtle, and the patients may appear to have normal extraocular motility. Careful motility evaluation, including dissociated cover and uncover testing, can differentiate true ophthalmoplegia from a cranial nerve palsy (Fig. 17.12).

Patients with cranial nerve palsies must undergo urgent neuroimaging, neurology consultation, and spinal fluid evaluation for pan culture and cytology. Cranial nerve palsy may have a vascular (typically ischemic), infectious (if the patient is septic and febrile), infiltrative (leptomeningeal disease, involvement of cancer), or other cause. If magnetic resonance imaging is negative but suspicion is high for leptomeningeal disease, cytologic evaluation of specimens obtained from three spinal taps should be performed.

Optic nerve swelling can occur for a variety of reasons, and the differential for it, like that described above for cranial nerve palsies, is broad. The focus of workup for optic nerve swelling depends on the patient's active medical conditions, including the cancer status. A patient with optic nerve edema may present with no symptoms, nonspecific blurred vision, or transient obscuration of vision (amaurosis fugax), which is a transient ischemic attack requiring stroke workup. Vision loss in patients with optic nerve edema may be profound or minimal with or without an obvious visual field deficit, and the prognosis for it depends on the underlying etiology.

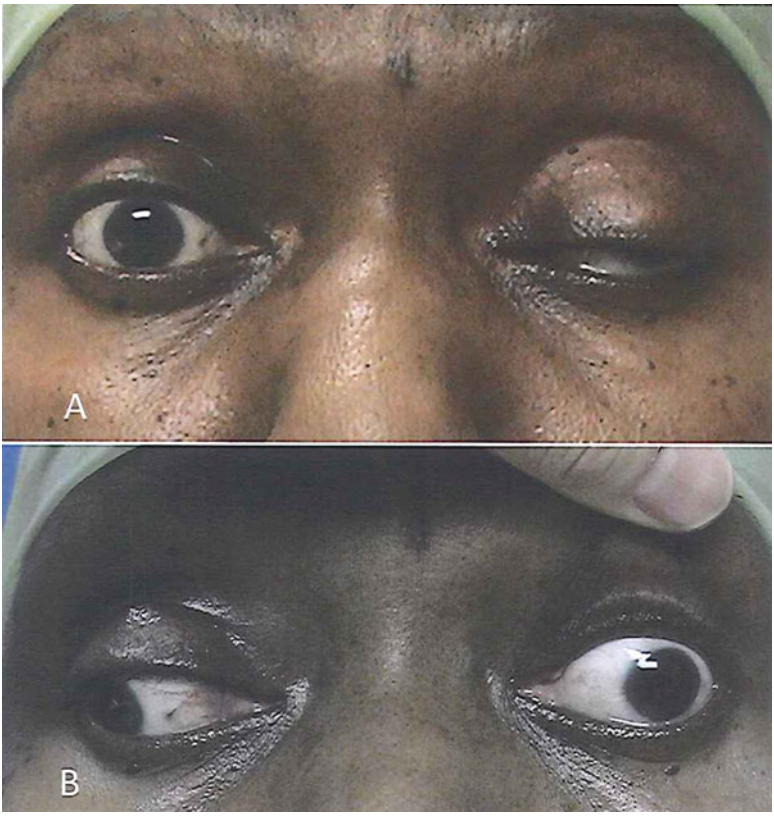

Fig. 17.12 (**a**) A patient presenting with ptosis. (**b**) The same patient with diplopia with the affected eyelid retracted on right lateral gaze. The patient had third cranial nerve involvement of leptomeningeal disease

Just as cancer patients are susceptible to infections, they are also prone to vascular problems given their generalized hypercoagulable state. Ischemic attacks can occur at the level of the ophthalmic or retinal vessels. The retinal vein can be occluded, which can result in moderate to severe loss of vision and optic nerve edema (Fig. 17.13), whereas central retinal artery occlusion can manifest as profound loss of vision (classic "cherry red spot" of the macula against a white ischemic retina) without optic nerve swelling. Patients with these two types of occlusion undergo similar workup, including infectious, infiltrative, and inflammatory workup for their vascular events, and their visual prognoses are guarded. Anticoagulation therapy must be considered in the context of the risks and benefits for a given patient as they relate to other medical comorbidities.

Optic neuropathy results from radiation toxicity. The workup for it is similar to obligatory imaging and cerebrospinal fluid analysis, although careful attention is given to the dose and location of previous external radiation treatment (orbital, intracranial, cavernous sinus, etc.). Even though a retrospective study demonstrated

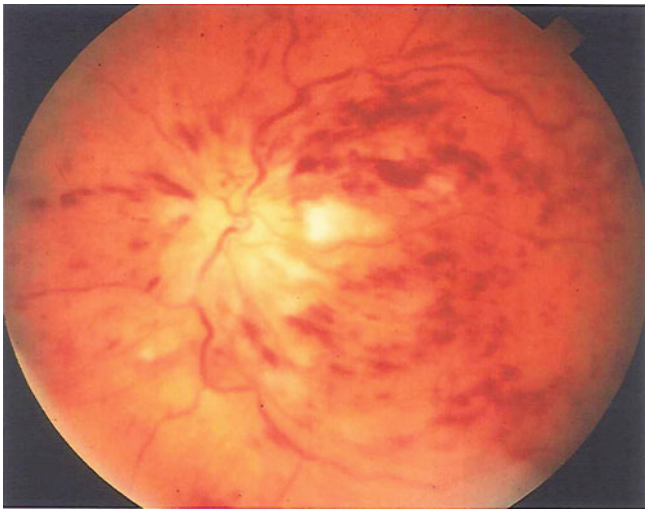

Fig. 17.13 Relapsed lymphoma presenting as optic nerve infiltration and central retinal vein occlusion

the threshold for optic nerve tolerance of irradiation, radiation-induced optic neuropathy and/or papillitis may occur below that threshold when patients have medical comorbidities (vasculopathy, diabetes, hypertension, etc.). Physicians have given high-dose steroids and hyperbaric oxygen and performed plasmapheresis for radiation-induced optic neuropathy with varying success, and the overall likelihood of visual recovery is poor.

When bilateral optic nerve swelling (papilledema) occurs, the intracranial pressure must be carefully evaluated by documenting the opening pressure during a lumbar puncture (Fig. 17.14). Symptoms include blurred vision, transient obscuration of vision, diplopia, headaches, nausea, and vomiting. Workup for papilledema in cancer patients is similar to that for cranial nerve deficits as described above in that cancer relapse must be ruled out along with other possible causes, such as infectious, infiltrative, vascular (sagittal sinus thrombosis), and medication-related (steroids) causes. Depending on the level of dysfunction (e.g., vision loss, visual field deficit, sixth nerve palsy) and of intracranial pressure, patients may be given oral medications to reduce the intracranial pressure while addressing the underlying etiology of the swelling (relapsed disease, infection, steroids, etc.). If the symptoms and deficits are severe, shunt placement may be necessary. If left untreated, papilledema owing to high intracranial pressure will lead to blindness and may result in other devastating neurologic events. Expeditious evaluation, workup, and treatment are crucial to preserving vision, reversing vision loss, and preventing other neurologic sequelae.

Optic nerve dysfunction may occur without any clinical evidence of an intraocular pathology. This may involve the optic chiasm, optic tract, or occipital lobe of the brain. A formal visual field examination may uncover bitemporal visual field deficits

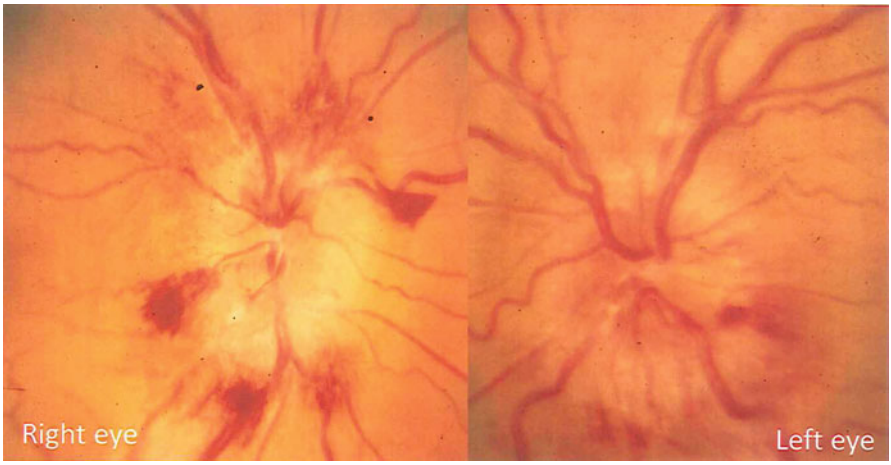

Fig. 17.14 Papilledema in a patient with double vision owing to sixth nerve palsy caused by high intracranial pressure induced by use of a high-dose steroid

(owing to pituitary problems) or homonymous hemianopsia or quadrantanopia. In patients with known intracranial lesions, visual field deficits are typically caused by the lesions, although patients may report that their deficits occurred only after treatment (surgery or irradiation). Pretreatment visual field examination can help patients understand their visual deficits prior to surgery or irradiation. In cancer patients without a history of metastatic disease who have visual field deficits, urgent neuroimaging can uncover new intracranial metastatic lesions or stroke. Regardless of the underlying etiology, however, recovery from visual field deficits is unlikely.

Conclusion

Many ophthalmologic emergencies are unique to cancer patients owing to their immune status, hypercoagulability, medication needs, and cancer. Symptoms of ocular emergencies can range from minimal to devastating visual loss. Physicians should have a high index of suspicion for ocular emergencies in patients with cancer who are undergoing treatment, have neutropenic fever, and/or are immunosuppressed after allogeneic SCT. Prompt ophthalmologic evaluation can aid in the diagnosis and treatment of blinding diseases in cancer patients.

Key Practice Points

- Ocular emergencies in cancer patients are often infectious in nature because of their immune status.

- Ocular side effects of cancer treatment are relatively common and typically not eyesight-threatening. However, symptoms alone may not correlate with the severity of ocular conditions. Some ocular emergencies may not initially cause vision changes.
- Timely ocular evaluation is crucial to the early detection and treatment of potentially blinding conditions, particularly infectious pathologies.
- Ocular signs and symptoms may be the first indications of recurrence of cancer. Therefore, certain ocular findings require workup for cancer recurrence.

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